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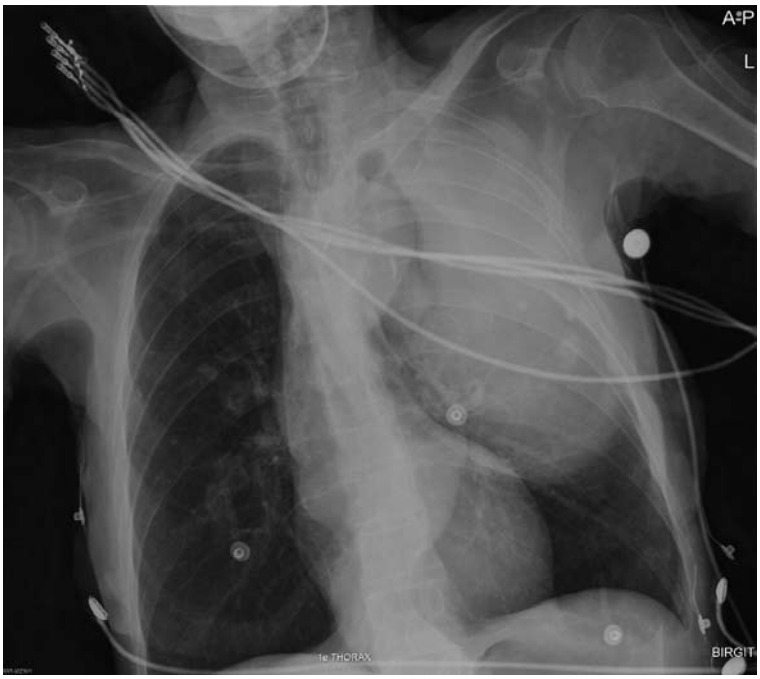

PHOTO QUIZ: A 75-year-old woman presenting to the emergency department with backache and respiratory distress, see page 444

November 2008, Vol. 66, No. 10, ISSN 0300-2977

VAN ZUIDEN COMMUNICATIONS

IF 1.548

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EDITORIAL

Beyond science: the salt debate

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INTRODUCTION

Man is the only mammal that consumes large amounts of salt. It is also the only species in which hypertension occurs. Obviously there is a relation between these two facts. Indeed, the internist Professor Borst from Amsterdam put forward experimental proof for this notion. By expelling salt with (imperfect) diuretics, patients with even severe hypertension were cured.[1] Later, in an exemplary experimental set-up2 he showed that a salt-retaining substance (liquorice) caused hypertension, bringing a pathophysiological explanation as well. It is impossible to summarise briefly the huge amount of experimental and epidemiological data which have since confirmed the relation between salt and blood pressure. Yet, despite overwhelming evidence, salt restriction as the basis of hypertension treatment has not gained general acceptance. The reasons of this deplorable development are the subject of this editorial.

SALT REDUCTION

In (hypertensive) patients

First of all, two aspects need to be distinguished: one is the use of salt restriction in patients with hypertension, and the other is salt restriction as a preventive health measure for the whole population.

While nobody denies the desirability of salt restriction for hypertensive patients, physicians do not actually implement it (any more). One explanation is that only half of the patients are 'salt sensitive'. Nevertheless this measure also increases the sensitivity for most antihypertensive drugs and makes them more effective.

The main reason for the neglect of salt restriction is doubtlessly the overpowering promotion campaigns for new antihypertensive drugs, which constitute huge economic interests. But indolence of doctors and patients is also an important factor. It is easier to prescribe a pill than to follow a diet or to explain the necessity of salt restriction in time-consuming talks. Changes in the doctor-patient relation are probably influential: patients have become more 'independent' and doctors feel less responsibility as 'providers for the health consumers'.

In practice, it is also difficult to obtain food that is low in salt. In the USA, this is virtually impossible.

As a result of these developments a large number of hypertensive patients receive insufficient treatment although the means for it are available. Most serious is the fact that patients without renal function on dialysis treatment cannot get rid of the salt they ingest with 'normal' food. Thus their body fluid expands with many litres between two dialyses, which have to be removed by rapid 'ultrafiltration'. As this is often only partly successful, they remain volume expanded and hypertensive. In contrast, a strategy based on effective salt restriction can achieve normal blood pressure without drugs in 90% of the patients and so decreases cardiovascular mortality.[3]

In the general population

While there is no fundamental difference in opinion about the effect of salt on established hypertension, large controversies exist around the desirability of salt restriction as a measure of general health. Although there are many indications that this could prevent development of hypertension, strict 'evidence-based' proof is lacking. It is then quite amazing how emotional the debate often becomes.

In 1984, the American Food and Drug Administration concluded that moderate salt restriction provides important advantages, while there are no indications that this would have any untoward effects on health. Norwegian and British committees gave similar recommendations. Hereupon, a group of distinguished hypertension experts published a letter in the Lancet,[4] in which they called the advice 'irresponsible and misguided'. They accused the advocates of salt restriction of pursuing an 'evangelical crusade'.

A worldwide investigation in 1988, the Intersalt Study[5] did not bring the expected solution. While it confirmed the

absence of hypertension in primitive communities with very low salt intake, initially a clear relationship between salt and blood pressure was not reported in the rest of the world. However, a subsequent analysis[6] showed a strong correlation and concluded that 'the results support the recommendation of salt restriction to prevent and control hypertension'.[7] Following this, the Salt Institute made its own analysis which came to the opposite conclusion.[8]
The influential journal 'Science' also joined the battle, calling it 'the longest, most vitriolic and surrealistic discussion in medicine'. The author of this blunt article accused supporters of salt restriction of being short-sighted, unscientific and politically motivated.[8]

INFLUENCE OF DIFFERENT INDUSTRIAL COMPANIES

From these examples it appears obvious that non-scientific 'lobbies' are also active in the field. Their tactics are to spread doubt, just like the tobacco and sugar industies once did. It was clear that the salt industry was able to engage researchers and subsidise articles supporting their interests. Also the pharmaceutical industry may not acclaim salt restriction, as this will reduce the need for blood pressure lowering drugs. Then there is the beer and soft drink industry, which, out of well-considered self-interest, has invested in chips and other salty snacks. Indeed, it was recently shown that salt intake, by stimulating consumption of soft drinks, increases obesity in childern.[9]
But the most important participant in this issue is the food industry. In our Western society, nearly 90% of ingested salt comes from prepared food (including bread). The consumer is not aware of that, which makes effective salt restriction virtually impossible. Therefore the advice often given by doctors of 'not to add salt to the food' can reduce intake by only 10 to 15%, which is definitely insufficient. Understandibly, the industry has no interest in reducing the salt content of their products.[10] If a tin of vegetables contains a little bit more salt than that of the competitor, it will be found more 'tasty'. Not surprisingly, a proposal in the English parliament to oblige the industry to mention the salt content on their products was initially blocked by the conservative party.

THE LOBBY FOR THE REDUCTION OF SALT IN FOOD PRODUCTS: 'CASH AND WASH'

It is the big merit of the English internist-investigator Graham MacGregor to have succeeded, despite these difficulties, to bring about a reduction in the salt content of many nutritients. He realised that the 'need' for salt is a habit (a mild form of addiction) that can be changed by gradual reduction in the salt content of the food consumed. He calculated that with a modest reduction in the current 15 grams (about 255 mmol sodium) to 9 grams NaCl daily (about 153 mmol sodium), 70,000 cases of stroke and heart attack could be prevented in the UK.[11]

Recently, strong support for the benefit of general salt reduction was provided by an investigation by Cook *et al.*[12] In a long-term follow-up of two groups of borderline hypertensive but otherwise healthy individuals who had been comprehensively counselled on reducing salt intake, cardiovascular events were 25% lower than in controls. Most remarkable was their observation that this was independent of the drop in blood pressure. It thus appears that even moderate salt reduction (the observed decreases were 44 and 33 mmol/day) has a favourable influence on health. It is beyond the scope of this editorial to speculate on the pathophysiological explanation of this finding.

In 1996, the Consensus Action on Salt and Health (CASH) was started.[13] Here, a group of specialists worked together with the aim to inform the food industry, the Government, other health professionals and even the whole population about the harmful effects of salt and bring about a reduction of salt consumption. They have since been successful in getting many supermarkets and manufacturers to adopt a policy of gradually reducing the salt content of their products and the government to finance a campaign to raise awareness of the effects of salt on health. Last year, they reported that the mean daily salt consumption in the UK had decreased by 0.5 grams. In the most recent newsletter daily salt was reduced from 9.5 to 8.6 grams daily.[14]

In 2005, World Action on Salt and Health (WASH) was launched with the aim to replicate the same progress in other countries. At present, 334 members from 80 countries have registered and this year 21 countries actively participated in a 'salt awareness week'. It should be realised that a change in lifestyle of the population cannot be accomplished by declarations of experts alone, but needs a lot of coordinated effort.

CONCLUSION

Finally, what are the implications of these developments for the Netherlands? A task force 'Salt in Foods' was established in order to stimulate the industry to reduce salt in their products (www.worldactiononsalt.com). Some individual initiatives are going on, but to be effective a Dutch WASH committee should be formally established in which physicians, dieticians and other health professionals,

nonprofit patient organisations and politicians participate. Financial support to maintain a secretariat should be obtained. Special responsibility rests with the Kidney Foundation and the Dutch Heart Foundation. From a scientific point of view the Dutch Hypertension Society should give support to the initiatives in the Netherlands.

The long history of salt sketched above may seem frustrating, but renewed attention and energy have resulted in recent successes illustrating that with dedication and perseverence, miracles can still happen. And the citation from the Plutarch, as translated in the book written by Denton, that 'first there is salt without which practically nothing is eatable'[15] is no longer believed to be the true with regards to our daily food.

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REVIEW

Rituximab in minimal change nephropathy and focal segmental glomerulosclerosis: report of four cases and review of the literature

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ABSTRACT

Minimal change nephropathy (MCNS) and focal segmental glomerulosclerosis (FSGS) are the main causes of the idiopathic nephrotic syndrome. MCNS usually responds to steroids and the long-term prognosis is generally good. However, some patients require prolonged treatment with immunosuppressive agents. FSGS generally follows a less favourable course: patients do not always respond to steroids and may progress to end-stage renal disease. Recurrence of FSGS after renal transplantation is frequently observed and may result in graft loss.

Recently, anecdotal case reports have described long-term resolution of nephrotic syndrome due to MCNS or FSGS after treatment with rituximab. We present four patients with nephrotic syndrome due to MCNS, FSGS or recurrence of FSGS after kidney transplantation, who were treated with rituximab with variable success. A review of the recent literature suggests that anti-CD20 antibodies may be a promising therapy, especially for patients with MCNS or idiopathic FSGS. Controlled studies are required to determine the efficacy of rituximab and to define which patients will benefit.

KEYWORDS

Focal segmental glomerulosclerosis, minimal change disease, nephrotic syndrome, recurrence, rituximab

INTRODUCTION

Minimal change nephropathy (MCNS) and focal segmental glomerulosclerosis (FSGS) are the main causes of the idiopathic nephrotic syndrome.

MCNS is typically seen in children with a nephrotic syndrome. Patients with MCNS usually respond to treatment with prednisone. However, in 40 to 50% of all patients the disease runs a frequently relapsing course, often requiring additional immunosuppressive treatment with agents such as cyclophosphamide or cyclosporine. The long-term prognosis is generally good, but up to 25% of frequent relapsers may need prolonged treatment with two or more immunosuppressive agents.[1] Cytokine release by T cells is supposed to play a key role in the pathogenesis of MCNS.[2] FSGS is considered less benign.[3] Patients do not always respond to steroid treatment and may progress to end-stage renal disease. Relapse of focal segmental glomerulosclerosis after renal transplantation is observed in 30 to 50% of all patients. In most cases, proteinuria recurs within two to four weeks after renal transplantation. If untreated, graft loss will occur.[4] FSGS is believed to be caused by a thus far unidentified circulatory permeability factor.[5,6]

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen which is present on B cells. Treatment with rituximab has been successful in patients with B cell lymphomas as well as in patients with autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or immune complex glomerulonephritis such as membranous nephropathy.[7-10] Recently several case reports have suggested that rituximab may be effective in the treatment of patients with MCNS and FSGS. In this report we describe four patients with a nephrotic syndrome due to MCNS or FSGS who were treated with rituximab because of failure of or intolerance to the standard immunosuppressive therapy. The short-term outcome of two patients has previously been described.[11,12] We also provide a review of the literature concerning the treatment of MCNS and FSGS with rituximab.

CASE REPORTS

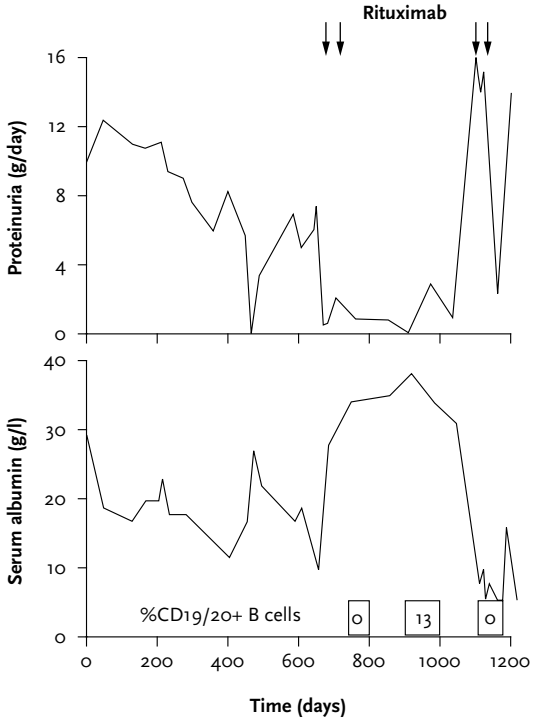
Patient 1: MCNS

The medical history of this 20-year-old female patient and the short-term efficacy of rituximab has been described.[12] At the age of 2 years, she presented with nephrotic syndrome which responded to high-dose prednisone. However, the subsequent course was characterised by frequent relapses during childhood, despite treatment with various immunosuppressive therapeutic regimens consisting of prednisone, cyclophosphamide or cyclosporine. At the age of 18 years, the nephrotic syndrome was under control with the use of a low dose of prednisone (5 mg every other day) in combination with mycophenolate mofetil (MMF 1000 mg twice daily) and tacrolimus (target trough level 5 to 10 mg/l). Thereafter, the patient again developed relapses necessitating higher doses of prednisone. Ultimately remission could only be attained with very high doses of prednisone (60 mg/day). Heavy proteinuria (10 g/day) and low serum albumin (12 g/l) persisted while she was on prednisone (20 mg/day), MMF (1000 mg twice daily) and tacrolimus (15 mg twice daily, target trough level of 8-12 mg/l). This condition lasted more than a year and became intolerable. Therefore we decided to treat the patient with rituximab. She received two doses of 1000 mg intravenously with a two-week interval; MMF was stopped. Within two weeks there was a remarkable decrease in proteinuria (2 to 3 g/day) and an increase in serum albumin (21 g/l). Tacrolimus and prednisone were tapered and discontinued. Four months after the administration of rituximab, proteinuria was below 1 gram per day (*figure 1*). Return of CD20+ cells was observed after nine months. A relapse occurred 13 months after treatment with rituximab. Low-dose prednisone was not effective and the patient was again treated with rituximab (1000 mg, with a two-week interval). Administration of the first dose resulted in depletion of CD19+ and CD20+ B cells within two weeks. No adverse events occurred. However, during administration of the second dose of rituximab, she almost immediately developed hypotension, fever and dyspnoea. Antichimeric antibodies directed against rituximab proved positive. Despite B-cell depletion, heavy proteinuria (10 g/day) and a low serum albumin (6 g/l) persisted. The patient is currently being treated with pulse methylprednisolone (3 g intravenously), tacrolimus (7 mg twice daily, target trough level 5 to 10 mg/l) and oral prednisone (10 mg/day). Serum albumin is 16 g/l and proteinuria 4 g/day. The clinical course is complicated by a recurring erysipelas.

Patient 2: FSGS

This male patient with FSGS was treated with rituximab at the age of 20 years. At the age of 12 years, he presented with a nephrotic syndrome due to biopsy-proven FSGS. Treatment with prednisone (60 mg/m^2) was initiated. After several weeks, cyclosporine was added because of persisting proteinuria and prednisone was replaced by mycophenolate mofetil. One year after presentation, proteinuria was 1 g/day and serum creatinine 90 µmol/l. At the age of 16 years, the patient again developed nephrotic range proteinuria. Cyclosporine was replaced by tacrolimus, leading to a temporary decrease in proteinuria but a rise in serum creatinine (140 µmol/l). A renal biopsy, performed three years after starting tacrolimus, showed 80% sclerosed glomeruli and moderate tubulointerstitial fibrosis. Tacrolimus was discontinued because of presumed toxicity and pulse methylprednisolone was administered (3 g intravenously) followed by oral prednisone (20 mg/day) with beneficial effects on proteinuria but not on serum creatinine. Renal function deteriorated and seven years after presentation serum creatinine was 170 µmol/l. At the age of 19 years, a relapse occurred during treatment with prednisone (10 mg/day) and mycophenolic acid (360 mg three times a day). Treatment with high doses of prednisone (60 mg/day) was initiated. This led to a complete remission, but during tapering of prednisone (to 25 mg/day) the patient experienced a relapse. We therefore decided to start treatment with anti-CD20 in this young male with high-dose steroid-responsive FSGS. Treatment consisted of two doses of rituximab (1000 mg intravenously) with a two-week interval. After the first dose of rituximab, mycophenolic acid was stopped and prednisone was continued in a dose of

Figure 1. *Course in terms of proteinuria and serum albumin and response to treatment with rituximab in patient 1, %CD19/20+ B cells is given*



10 mg/day. Nephrotic range proteinuria persisted. Serum creatinine remained stable for six months but then renal function rapidly deteriorated necessitating renal replacement therapy.

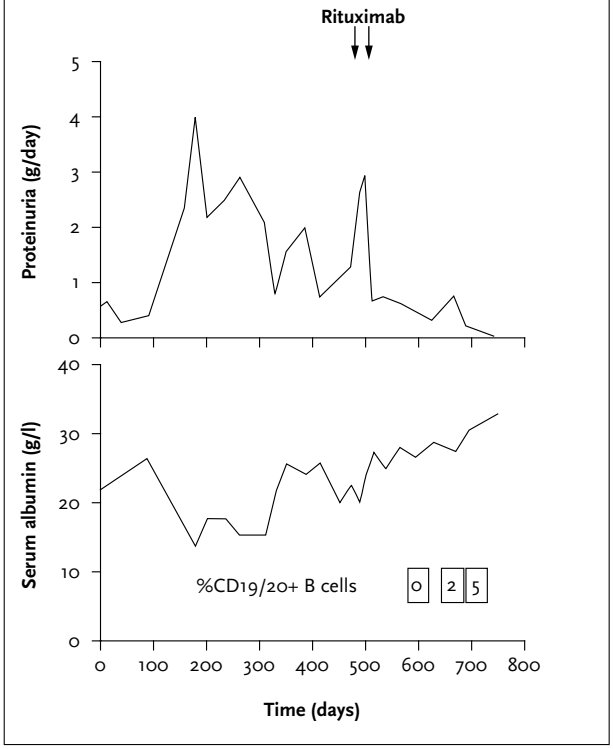
Patient 3: FSGS

This 15-year-old male was treated with rituximab because of relapsing nephrotic syndrome due to FSGS. The patient presented with a nephrotic syndrome at the age of 7 years. A renal biopsy showed FSGS. Immunosuppressive treatment was started with cyclosporine and prednisone. Proteinuria gradually decreased and eventually a partial remission was attained. Three years after presentation a relapse occurred. Several courses of methylprednisolone (750 mg/day for three days) were given and mycophenolate mofetil was added to the immunosuppressive regimen. A partial remission was attained, but after six months a relapse occurred. High-dose prednisone therapy again led to a partial remission. Prednisone therapy was tapered and MMF was discontinued due to recurrent respiratory infections. Eventually cyclosporine was tapered and discontinued. At the age of 12, nephrotic range proteinuria recurred and the patient was treated with intravenous methylprednisolone, followed by prednisone and cyclophosphamide (2 to 3 mg/kg/day for 12 weeks). Partial remission was attained but tapering of prednisone to 25 mg every other day led to a rise in proteinuria. A renal biopsy performed six years after presentation showed 40% sclerosis of glomeruli and minor tubulointerstitial damage. Because of persisting proteinuria triple therapy was started at the age of 15. While on prednisone (tapered to 40 mg/day), MMF (1000 mg twice daily) and tacrolimus (5 mg twice daily, target trough level 7 to 10 mg/l), the patient experienced a relapse. Treatment with rituximab was started (1000 mg intravenously at a two-week interval). No adverse events occurred. Approximately one month after receiving the first dose of rituximab, a profound decrease in proteinuria (2.11 g/l to 0.31 g/l) combined with an increased serum albumin (26 g/l to 34 g/l) was observed (*figure 2*). Six months after receiving rituximab, CD19 and CD20 positive B cells were detected. Currently, ten months after the administration of rituximab, the patient has attained a complete remission while receiving minor doses of prednisone (3 mg every other day) and tacrolimus (2 mg twice daily).

Patient 4: recurrent FSGS after renal transplantation

The case report of this patient has been described by Deegens *et al.*[11] At the age of 10, she presented with a nephrotic syndrome due to biopsy-proven FSGS. End-stage renal disease developed despite treatment with prednisone, cyclophosphamide and cyclosporine. At the age of 13 she received her first renal graft. Recurrence of FSGS led to graft failure after one year. Seven years later, she received a second renal graft. Baseline immunosuppressive therapy consisted of prednisone (10 mg), tacrolimus (target trough level 15 to 20 mg/l) and mycophenolate mofetil (750 mg twice daily). There was almost immediate graft function. One week after transplantation, the patient developed nephrotic range proteinuria. Because of a presumed recurrence of FSGS, plasma exchange (PE) was started which resulted in complete remission. Proteinuria recurred, however, three months after cessation of PE while the patient was on prednisone (15 mg) and tacrolimus (target trough level 5 to 10 mg/l). A second course of PE (eight sessions) again resulted in complete remission. A third relapse occurred two years later. A biopsy of the renal graft demonstrated diffuse foot process effacement, without significant lesions on light microscopy and immunofluorescence, supporting a diagnosis of recurrent FSGS. A remission of proteinuria could only be maintained with continuous PE, even though the patient was treated with a more intensive immunosuppressive regimen consisting of prednisone (10 mg), tacrolimus (target trough level 5 to 10 mg/l), and MMF (500 mg twice daily), which was replaced by azathioprine (2 mg/kg/day) because of gastrointestinal side effects. Given PE dependence, it was decided to start treatment with rituximab. Apart from a temporary neutropenia, no significant side effects occurred during the course of four weekly infusions (375 mg/m^2). After treatment

Figure 2. *Course in terms of proteinuria and serum albumin and response to treatment with rituximab in patient 3, %CD19/20+ B cells is given*



B-cell markers CD19+ and CD20+ were undetectable. Increasing proteinuria required three PE sessions during the first four months after treatment with rituximab. Thereafter, proteinuria gradually decreased without further interventions. Seven months after treatment with rituximab a partial remission (proteinuria <2 g/day) was attained. Nine months later, she experienced a relapse of proteinuria. At that time CD19+ and CD20+ B cells were still undetectable. The patient was again treated with a single infusion of rituximab 1000 mg. Proteinuria gradually decreased and a partial remission was reached two months after treatment

DISCUSSION

We have described our experience with rituximab therapy in four patients with a nephrotic syndrome due to MCNS or FSGS. These cases suggest that rituximab may be effective in patients with nephrotic syndrome due to MCNS or FSGS. Admittedly, our data are anecdotal and controlled studies are required to prove the efficacy of rituximab. Nonetheless, we were impressed by the response in cases 1 and 3. These patients needed continuous treatment with various immunosuppressive agents for many years and ultimately remained severely nephrotic despite triple therapy with a calcineurin inhibitor, mycophenolate mofetil and prednisone. Following treatment with rituximab they developed a (nearly) complete remission while using no (case 1) or a limited dose (case 3) of immunosuppressive agents. In case 4, rituximab also appeared effective, although a response occurred slowly (after five months) and a contribution of plasmapheresis could not be excluded. The response to rituximab monotherapy after relapse, however, basically proved its efficacy. As illustrated by patient 2 and numerous case reports in the recent literature (*tables 1* to *3*), success varies. Furthermore, our cases illustrate a number of issues that may arise during treatment of nephrotic syndrome with rituximab, such as the relationship between proteinuria and circulating B cells and the potential development and role of antichimeric antibodies. We will discuss some of these issues briefly, after reviewing the literature on the treatment of nephrotic syndrome with rituximab.

MCNS

Table 1 provides an overview of the use of rituximab in patients with MCNS.[13-17] These reports have included both children and adults with a frequently relapsing nephrotic syndrome necessitating continuous immunosuppressive therapy. In all patients rituximab treatment resulted in a partial or complete remission of the nephrotic syndrome within two to ten weeks. In some patients concomitant immunosuppression could be stopped. In the study by Francois *et al.* remission was maintained while continuing intermittent administration of rituximab.[14] Gilbert *et al.* successfully treated a relapse with a new course of rituximab.[13] In contrast, our patient did not respond to a second course of rituximab after relapsing. Of note, in our patient treatment was not given according to protocol due to the development of antibodies causing serum sickness.

FSGS

The first case suggesting benefit from rituximab in FSGS was described in 2004. In this 16-year-old boy, the diagnosis of FSGS was made when he was 2 years of age and its clinical course was characterised by multiple relapses, despite treatment with steroids, cyclosporine, cyclophosphamide and tacrolimus. Finally, he became severely dependent on steroids. Subsequently, the diagnosis of idiopathic thrombocytopenic purpura (ITP) was made in this patient. Neither steroids nor immunoglobulins induced permanent remission and it was decided to treat the ITP with rituximab. After treatment with rituximab no relapse of proteinuria or thrombocytopenia occurred. Since then, several case reports have described the effect of rituximab in FSGS.[16,18,19] So far, six patients (all children) with FSGS in their native kidney have been described, all of whom have been successfully treated (*table 2*). However, one must be aware of publication bias, since positive outcomes are more likely to be reported than negative ones. As illustrated by patient 3, treatment may fail. This could be due to the presence of irreversible damage before treatment with rituximab, considering the fact that renal biopsy showed 80% sclerosed glomeruli. Successful treatment with rituximab of a patient with FSGS and a diminished renal function has been described.[19]

Recurrence of FSGS after transplantation

Thus far, 15 patients (including patient 4) with recurrent FSGS after transplantation who received rituximab have been described.[20-28] An overview is given in *table 3*. These data suggest that response is variable and less favourable than in patients with MCNS or FSGS in their native kidneys. Moreover, interpretation of these data is difficult. In some patients who were treated successfully, rituximab was given to treat a coexisting posttransplant lymphoproliferative disorder (PTLD). It cannot be excluded that in these patients development of FSGS was related to the PTLD. In other patients rituximab was given in combination with plasmapheresis, making it impossible to draw conclusions on the efficacy of rituximab solely. On the other hand, response to rituximab may be slow as observed in patient 4, and consequently overlooked. Yabu *et al.* described a patient who did not respond within two months and received a short course of plasmapheresis. Thereafter proteinuria decreased from 6 to 1.9 g/day. In our

Table 1. *Rituximab in patients with minimal change nephropathy*

Author	Sex	Age at diagnosis (years)	Age at start RTX (years)	RTX dose	Concomitant therapy	Response	Duration of follow-up	Comments
Gilbert	F	1.5	15	375 mg/m² once weekly, 4 doses	Deflazacort, tacrolimus	Remission, not specified	18 months	Relapse after 9 months. Response to steroids, relapse during tapering. After 16 months reinfusion (2 weekly doses), again remission. Ongoing treatment with low dose of prednisone
Francois	F	6	23	375 mg/m² once weekly, 4 doses	Prednisone, basiliximab (stopped before rituximab)	CR within 3 weeks	28 months	One year after first dose, reinfusion (2 weekly doses) because of detectable CD19/20 levels Persistent CR without immunosuppressive treatment
Smith	M	3	13	375 mg/m² once	Tacrolimus, MMF, prednisone	CR within 2 weeks	6 months	After 3 months return of CD19/20+ cells. Persistent CR, ongoing treatment with low doses of prednisone/ tacrolimus
Bagga	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR	14-58 weeks	Report of 5 patients with NS: 2 MCNS, 3 FSGS No differentiation between different patients possible. Ongoing treatment with prednisone and tacrolimus/CsA
	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR or PR	14-58 weeks	
Yang	F	40	40	375 mg/m² once weekly, 4 doses	Prednisone, MMF	CR within 10 weeks	12 months	CR, ongoing treatment with low doses of prednisone and MMF
Present study	F	2	20	1 g every other week, 2 doses	Prednisone, MMF, tacrolimus	PR within 4 weeks	16 months	PR for 12 months without immunosuppressive treatment. Relapse after 13 months, retreatment with RTX not effective

NS = nephrotic syndrome; MCNS = minimal change nephropathy; FSGS = focal segmental glomerulosclerosis; RTX = rituximab; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; CsA = cyclosporine; CR = complete remission; PR = partial remission; M = male; F = female; NA = not available.

Table 2. *Rituximab in patients with focal segmental glomerulosclerosis*

Author	Sex	Age at diagnosis (years)	Age at start RTX (years)	RTX dose	Concomitant therapy	Response	Follow-up	Comments
Benz	M	2	16	375 mg/m² once weekly, 4 doses	Prednisone, CsA	Remission, not specified	12 months	Treated for ITP, no relapses on CsA monotherapy
Bagga	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR	14-58 weeks	Report of 5 patients with NS: 2 MCNS, 3 FSGS No differentiation between different disease entities possible Ongoing treatment with prednisone and tacrolimus /CsA
	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR	14-58 weeks	
	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR or PR	14-58 weeks	
Nakayama	F	8	10	375 mg/m² once	Prednisone	CR within 8 months	14 months	PR after 1, CR after 8 months, no immunosuppressive therapy
	F	11	12	375 mg/m² once	Prednisone, CsA	PR within 1 month	14 months	Relapse after 8 months. After second course of RTX PR within 2 and CR within 5 months, ongoing treatment with prednisone
Present study	M	12	20	1 g every other week, 2 doses	Prednisone, MMF	None	7 months	80% of glomeruli showed sclerosis
	M	7	15	1 g every other week, 2 doses	Prednisone, tacrolimus, MMF	CR within 1 month	10 months	CR with low doses of prednisone and tacrolimus

NS = nephrotic syndrome; MCNS = minimal change nephropathy; FSGS = focal segmental glomerulosclerosis; ITP = idiopathic thrombocytopenic purpura; RTX = rituximab; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; CsA = cyclosporine; CR = complete remission; PR = partial remission; M = male; F = female; NA = not available.

Table 3. *Rituximab in patients with recurrent FSGS after transplantation*

Author	Sex	Age at RTX treatment (years)	RTX dose	Concomitant therapy	Previous plasma exchange	Response	Follow-up (months)	Comments
Pescovitz	M	7	375 mg/m² once weekly, 6 doses	Tacrolimus, MMF (daclizumab)	Yes, response?	PR within 2 months	16	Treatment with rituximab because of PTLD
Nozu	M	12	375 mg/m² once weekly, 4 doses	CsA	No	CR within 7 months	36	Treatment with rituximab because of PTLD
Gossman	F	48	375 mg/m² once weekly, 2 doses	Prednisone, tacrolimus, MMF, ATG	Yes, no response	CR within 1.5 month	12	
El Firjani	F	48	375 mg/m² 6 doses in 8 weeks	Prednisone, tacrolimus, MMF, ATG	Yes, no response	None	NA	
Hristea	M	22	375 mg/m² once weekly, 2 doses	Prednisone, tacrolimus, MMF, basiliximab	Yes, partial response	CR after 3 months	24	PE and RTX were given concomitantly
Kamar	M	25	375 mg/m² once weekly, 2 doses	Prednisone, CsA, MMF, basiliximab	Yes, pre-emptive, partial response	CR within 1 week	10	PE and RTX were given concomitantly A relapse (within 1 month!) was also treated with RTX and PE
	M	46	375 mg/m² once weekly, 4 doses	Prednisone, CsA, MMF	Yes, no response	None	4	Proteinuria had already decreased before RTX was given
Marks	M	6	375 mg/m² once weekly, 4 doses	Prednisone, tacrolimus	Yes, but incomplete due to infections	None	5	No complete B-cell depletion
	M	10	750 mg/m² every other week, 2 doses	Prednisone, tacrolimus, MMF	Yes, partial response	None	14	No complete B-cell depletion No remission but stable at once weekly PE
Meyer	F	31	375 mg/m² once weekly, 3 doses	Prednisone	Yes, pre-emptive partial response	PR	14	One weekly dose not given because of UTI, decrease of proteinuria 5 months after RTX
Yabu	M	41	1 g every other week, 2 doses	Prednisone, tacrolimus, MMF	Yes, partial response	PR within 4 months	12	Received PE 2 months after RTX
	F	43	375 mg/m² once weekly, 4 doses	Prednisone, tacrolimus, MMF, ATG	Yes, partial response	None	10	Dialysis after 7 months, transplant nephrectomy after 10 months
	F	41	375 mg/m² once weekly, 4 doses	Prednisone, MMF, CsA, ATG, total lymphoid irradiation	Yes, no response	None	7	Stable serum creatinine (88 µmol/l) and serum albumin
	F	47	375 mg/m² once weekly, 4 doses	JAK3 inhibitor, MMF, prednisone	Yes, partial response	None	8	Stable serum creatinine (140 µmol/l) and serum albumin
Present study	F	24	375 mg/m² once weekly, 4 doses	Prednisone, tacrolimus, azathioprine	Yes, partial response	PR within 7 months	24	Relapse after 16 months, after second course of RTX PR within 2 months

PTLD = posttransplant lymphoproliferative disorder; UTI = urinary tract infection; PE = plasma exchange; RTX = rituximab; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; CsA = cyclosporine; CR = complete remission; PR = partial remission; M = male; F = female; NA = not available.

opinion a positive effect of rituximab cannot be excluded in this patient. Of note, in two out of eight nonresponsive patients, complete B-cell depletion was not achieved. Lastly, successful treatment of patients with recurrence of FSGS and a severely diminished renal function has been reported.[24, 25]

Overall, our case studies and a review of the literature suggest that anti-CD20 therapy may expand the therapeutic arsenal for patients with MCNS or FSGS. Controlled trials are needed to determine the true value of such treatment and more information is needed in order to determine which patients are likely to benefit.

Immunoregulatory effects of B cells

Since FSGS and MCNS are not antibody-mediated diseases, the success of rituximab may seem surprising. However, B cells play an important role as immunoregulatory cells by both antigen presentation and cytokine release. Their elimination could have dampening effects on other immune cells such as T lymphocytes, dendritic cells, or macrophages. This hypothesis is supported by an observed reduction in activated T cells and a decrease in T-cell derived cytokines in patients with SLE and RA after treatment with rituximab.[29,30]

B-cell depletion and response

Administration of rituximab results in B-cell depletion. It is tempting to speculate that rituximab therapy may be monitored by measuring B cells. The data of our patients and those reported previously argue against an unambiguous relationship. Some patients do not respond despite B-cell depletion, others show a lack of correlation between the return of B cells and time of relapse. Similar observations have been made in patients with systemic diseases such as vasculitis or SLE.[9] From these studies it was suggested that measurement of circulating B cells does not accurately reflect the presence of B cells in other compartments, such as bone marrow, lymphoid tissue and organs. B cells residing in these nonperipheral compartments may be more resistant to depletion.[31] The presence of these residual cells could contribute to the disease and lead to a failure to respond or a relapse in the absence of circulating B cells. This phenomenon was observed in patient 4; no B cells were detected at the time of relapse of FSGS. Evaluation of the regeneration pattern of the subclasses of B cells after rituximab may also be important. In patients with RA, naive B cells returned within 12 months after treatment with rituximab, but CD27+ memory cells remained absent for a longer period of time.[32] This could explain why some patients remain in remission despite the return of B cells as is illustrated by patient 1 and other case reports.[15-19] Thus, monitoring of peripheral B cells cannot be used as an indication to repeat treatment with anti-CD20 antibodies, since the return of B cells does not appear to directly coincide with the return of disease activity. The decision to repeat treatment with rituximab should be based on clinical symptoms.

Kinetics of rituximab in proteinuria

In patients with non-Hodgkin's lymphoma (NHL), return of B cells was observed after six months and after 12 months B-cell counts had normalised in the majority of patients. Similar observations have been made in patients with RA. Fervenza *et al*. suggested that pharmacokinetic parameters may be different in patients with proteinuria since part of the administered antibody may be lost with protein-containing urine.[7] Rituximab levels were significantly lower in patients with idiopathic membranous nephropathy when compared with patients with RA. Indeed, in patients with idiopathic membranous nephropathy return of B cells was observed after three months and normalisation of B cells was observed after six months. However, there was no correlation between rituximab levels and proteinuria. In another study in patients with nephrotic range proteinuria, B-cell counts remained subnormal for 12 months.[8] Thus, it is premature to draw firm conclusions regarding the effect of proteinuria on rituximab pharmacokinetics. Moreover, the relationship between rituximab levels and B-cell depletion needs further study.

Development of antibodies against rituximab

Due to the relapsing course of many nephropathies, it is likely that many patients will need repeated courses of rituximab. As indicated by the case history of patient 1, frequent administration of rituximab may lead to the development of antibodies. Since rituximab is a chimeric mouse/human antibody, it is less immunogenic than mouse monoclonal antibodies. Still human antichimeric antibodies (HACA) can develop. The reported incidence of HACA development varies widely. In B-NHL patients, HACA have been found in only one of 166 patients treated in the pivotal study, and in four of the 90 patients treated in another study.[33,34] In contrast, HACA were observed in six out of 14 tested patients with idiopathic membranous nephropathy and in 11 out of 17 patients with SLE.[7,35] The clinical significance of HACA is controversial. The presence of HACA could be expected to lead to a decreased response to rituximab due to accelerated clearance, and an increased incidence of serum sickness. Some studies showed a lower efficacy of rituximab in the presence of HACA.[35,36] In several other studies, however, no correlation between HACA and clinical response or infusion reactions was observed.[7,10,37] Of note, one patient with relapsed lymphoma was successfully treated with a second course of rituximab, despite the presence of HACA.[38] Our patient clearly shows that HACA can be problematic. Further studies should evaluate if the development of HACA can be suppressed by using concomitant immunosuppressive therapy at the time of administration of rituximab. In patients with RA, development of antibodies against infliximab is reduced by the use of methotrexate.[39] New humanised versions of anti-CD20 antibodies may ameliorate the problem of antibody formation.

CONCLUSION

Although anti-CD20 antibodies seem to offer a perspective for the treatment of patients with nephrotic syndrome due to MCNS or FSGS, positive results should be viewed with the necessary caution, since they may be overestimated due to publication bias. Controlled studies must be performed to prove the efficacy of rituximab, to evaluate its cost-effectiveness

and to determine which patients will benefit. In the meantime it is important to establish guidelines for the rescue treatment of patients with steroid-dependent nephrotic syndrome. A nationwide registry could aid in finding early answers to some of the above-mentioned questions.

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Netherlands
The Journal of Medicine

REVIEW

Toxicity of contrast media: an update

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ABSTRACT

Renal toxicity of iodinated radiocontrast media (contrast-induced nephropathy; CIN) is a major cause of acute renal failure in hospitalised patients. Magnetic resonance imaging (MRI) is applied as an alternative technique but the use of gadolinium (Gd) containing contrast media carries the risk of nephrogenic systemic fibrosis (NSF), a potentially lethal disorder that occurs especially in patients with renal failure. In this article we give an update of the literature on toxicity of radiocontrast media and on preventive measures.

Risk of nephrotoxicity of iodinated contrast media can be reduced by identification of high-risk patients. In these patients pre- and post-hydration with isotonic saline should be applied. When there is insufficient time to prehydrate, a short infusion protocol with sodium bicarbonate is preferable. There is a lack of evidence to support the use of oral or intravenous N-acetylcysteine or iso-osmolar contrast media. In order to prevent NSF, linear gadolinium chelates should not be used in patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min. In patients with eGFR between 10 and 30 ml/min the small chance of NSF with cyclic Gd-containing chelates must be balanced against the high risk of developing CIN, and the morbidity and mortality associated with the start of dialysis. In patients without residual renal function, the small chance of developing NSF after macrocyclic Gd-enhanced MRI imaging may tip the balance to the use of iodine containing contrast media.

KEYWORDS

Contrast, gadolinium, nephropathy

INTRODUCTION

Iodinated radiocontrast media are frequently used in radiological procedures such as computerised tomography (CT) scans, angiography, and interventional cardiology procedures. These media can cause acute renal failure. Acute renal failure induced by radiocontrast media, which is known as contrast-induced nephropathy (CIN), is the third most common cause of new onset renal failure in hospitalised patients.[1] In patients undergoing coronary interventions, the incidence of CIN (defined as a rise in serum creatinine concentration of more than 25%) was 14.5% and the incidence of end-stage renal failure was 1.3%.[2] The development of CIN not only increases length of hospital stay but is also associated with an increased mortality rate.[3] Prevention of renal damage due to radiographic contrast media is one of the ten items in a national campaign to improve safety in Dutch hospitals. The optimal protocol for prevention of CIN has been subject of debate. Recently, the Dutch Institute for Healthcare Improvement, the CBO, has published guidelines for the prevention of CIN.[4] *Table 1* summarises the guideline proposals. From the guidelines it is evident that it is important to identify high-risk patients. The most important determinant of risk is baseline renal function. Patients with renal insufficiency are at highest risk of developing CIN.

Since the conception of the guidelines, results of several new studies on CIN have been published. Moreover, magnetic resonance imaging (MRI) is often advocated as an alternative to avoid CIN in patients with renal insufficiency. However, concern has risen about the toxic side effects of the gadolinium-containing contrast media used in MRI, especially the occurrence of nephrogenic systemic fibrosis (NSF).[5]

In this article we present an update on the toxicity of contrast media and preventive measures.

IODINATED CONTRAST MEDIA-INDUCED NEPHROPATHY

Iso-osmolar contrast media

Iodinated contrast media can be classified into three groups according to their osmolarity: high-osmolar

Table 1. *Summary of CBO guideline on prevention of radiocontrast nephropathy*

Low-risk patient		Withdraw diuretics and NSAID 24 hours before contrast exposure Instruct patients to take sufficient fluid and salt in order to prevent dehydration
High-risk patient	• Waldenstrom/Kahler disease with light-chain proteinuria • eGFR <45 ml/min/1.73 m² • eGFR 45-60 ml/min/1.73 m² with diabetes mellitus or two additional risk factors: peripheral vascular disease, heart failure, age >75 years, anaemia, symptomatic hypotension, high volume of contrast, dehydration, use of diuretics and/or NSAID	Pre- and post-hydration: NaCl 154 mmol/l; total amount 12 to 16 ml /kg before and a similar amount after contrast exposure. Infusion rate may be 250 ml/min, a lower infusion rate and/or a lower volume is indicated in patients with heart failure or severe renal failure (eGFR <20-30 ml/min) In case of emergency procedure: $NaHCO_3$ 154 mmol/l, 1 hour before at a rate of 3 ml/kg/h and for 6 hours after contrast exposure at a rate of 1 ml/kg/h

NSAID = nonsteroidal anti-inflammatory drug; eGFR = estimated glomerular filtration rate.

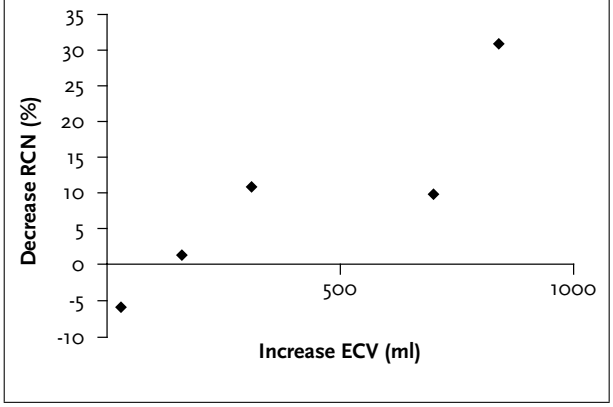
contrast media (HOCM, 2000 mOsm/kg), low-osmolar contrast media (LOCM 600-800 mOsm/kg) and iso-osmolar contrast media (IOCM 290 mOsm/kg). There is clear evidence that LOCM have a lower risk of CIN than the conventional HOCM.[6,7] In order to further reduce side effects, IOCM have been introduced. In a meta-analysis it was concluded that the risk of CIN was indeed lower after IOCM as compared with LOCM (OR 0.39).[8] However, analysis of the three studies that contributed to this result raises doubt on the validity of this conclusion.[9-11] None of these studies used an adequate pre- and post-hydration regimen. The study by Aspelin was performed in diabetics, and the patient groups were not completely matched: in the LOCM group duration of diabetes was five years longer. Also, glomerular filtration rate at baseline was probably lower in the LOCM group, which included a higher percentage of women and patients with a higher body weight. Several studies that were not included in this meta-analysis did not show a benefit of iso-osmolar contrast media.[12-14] The most recent study was published in 2007.[15] This was a randomised controlled trial that included 482 patients who underwent a cardiac angiography with or without an intervention. Subjects were randomised to receive either the low-osmolar agent iopamidol or the iso-osmolar agent iodixanol. All patients received an isotonic bicarbonate solution as preventive strategy (see below). No differences in CIN were noted between both groups. This study thus does not provide evidence of any advantage of IOCM either, although it cannot be excluded that differences between the various LOCM contribute to the divergent results. A pathophysiological explanation for the disappointing results of IOCM might be the impaired renal blood flow caused by an increase in blood viscosity that was demonstrated by *in vitro* animal studies.[16]

In conclusion: there is insufficient evidence that iso-osmolar contrast media are better than low-osmolar contrast media.

Hydration

There is almost unanimous agreement in the literature that appropriate hydration prevents contrast-induced nephropathy. It is therefore rather surprising that there are only a limited number of studies that support this conclusion. Hydration was compared with placebo in one study only.[17] Other studies have compared different hydration regimens consisting of (combinations of) isotonic saline, hypotonic saline or oral water given as bolus or continuous infusion.[18-21] We have analysed these studies and specifically examined the relation between the change in extracellular volume (ECV) and the treatment effect. We calculated the increase in ECV volume for a hypothetical patient, using a ratio of extracellular : intracellular volume of 1:2. Thus, for example, 1000 ml of isotonic saline increases ECV by 1 litre, whereas 1000 ml of water increases ECV by 0.33 litre. The difference in the incidence of CIN was correlated with the change in ECV (*figure 1*). From these data we can conclude that the best regimen is the one that most effectively increases extracellular volume. This can best be

Figure 1. *Relation between the change in extracellular volume (ECV; ml) and the decrease in contrast-induced cephropathy (CIN; %)*



done with isotonic saline, given in the hours before contrast medium infusion. Preferably, ECV should be increased by 500 to 1000 ml. The rate of hydration does not seem important for protection but should be governed by clinical factors that determine the risks of ECV volume expansion, such as heart failure and severe renal insufficiency.

A more practical protocol might be oral supplementation of NaCl instead of intravenous hydration. One study has indeed shown that oral NaCl in a dose of 1 g/10 kg bodyweight per day for 48 hours can be as effective as prehydration with isotonic saline at a rate of 15 ml/kg for six hours.[22] More studies are needed to document the feasibility of this outpatient protocol in routine practice.

N-acetylcysteine (NAc)

The use of N-acetylcysteine (NAc) for the prevention of CIN is heavily debated. The recent CBO guidelines concluded that there was insufficient evidence to support the routine use of NAc. Many have argued against this conclusion. New data were summarised in a recent meta-analysis. This meta-analysis included 30 trials in which NAc was used.[23] Although there was a significant subgroup heterogeneity, the authors concluded that NAc was more renoprotective than hydration. They advised the use of NAc in routine clinical practice, particularly since the oral administration of NAc is safe and extremely inexpensive. However, the data do not support this conclusion. The meta-analysis included 30 randomised controlled trials. Overall, CIN occurred in 229 of the controls and in 147 of the Nac-treated patients. This difference in event rate is fully explained by the results of nine trials. One study is published in abstract form only. The remaining eight trials are summarised in *table 2*.[24-31] It is evident that only two trials used NAc according to the standard protocol of orally administered NAc, 600 mg twice daily on the day before and after the procedure. Two studies used NAc intravenously, three trials administered oral NAc immediately before the procedure, and one study used a lower dose of NAc.

Furthermore, the meta-analysis of Kelly *et al*. did not include four studies that were included in the previous meta-analysis. Still, both meta-analyses used the same criteria for selection of the studies. Three of these studies did not show an advantage of NAc.

The latest meta-analysis adds to the list of the many meta-analyses on the role of NAc in preventing CIN. The conclusions have varied, and interpretation is difficult due to the heterogeneity of the included studies. It has been suggested that large randomised controlled trials (RCT) are required in order to prove beyond doubt the effectiveness of NAc. Thus far three RCT have been conducted that included more than 300 patients.[31-33] Unfortunately, these studies also differed in protocol. The study by Azmus *et al*. is the only in which oral NAc was used and added to a standardised pre- and post-hydration protocol. In contrast, Webb *et al*. used intravenous NAc and incomplete hydration, whereas Marenzi *et al*. used a combination of intravenous and oral NAc in patients that received posthydration only. In two studies no benefit of NAc was observed.[32,33]

In conclusion, there is insufficient evidence to incorporate the routine use of NAc either intravenously or orally on top of an adequate hydration regimen in the guidelines.

Sodium bicarbonate

It has been hypothesised that alkalisation of the urine by administration of sodium bicarbonate reduces pH-dependent renal generation of reactive oxygen species,

Table 2. *Overview of positive trials with N-acetylcysteine (NAc)*

Author (year)	Events in control group N (%)	Events in NAc group N (%)	Remarks
Tepel (2000)[24]	9 (21)	1 (2)	Standard hydration; standard NAc
Shyu (2002)[25]	15 (25)	2 (3)	Standard hydration; NAc 2 dd 400 mg
Diaz Sandoval (2002)[26]	13 (45)	2 (8)	Short hydration; one dose NAc 600 mg orally before procedure
Baker (2003)[27]	8 (21)	2 (5)	Hydration different between groups; NAc 150 mg/kg iv immediately before procedure, 50 mg/kg * 4 hours thereafter
Kay (2003)[28]	12 (12)	4 (4)	Hydration with NaCl 0.9%; standard NAc
MacNeill (2003)[29]	7 (32)	1 (5)	In outpatients short hydration (4 h) and 2 doses of 600 mg NAc within 4 hours before procedure
Ochoa (2004)[30]	11 (25)	3 (8)	Short hydration (150 ml/h * 4 h); NAc 1000 mg orally 1 hour before and 4 hours after procedure
Marenzi (2006)[31]	39 (33)	17 (15)	No prehydration; NAc 600 mg iv before, 2 dd 600 mg after procedure
		10 (8)	No prehydration; NAc 1200 mg iv before, 2 dd 1200 mg after procedure

Standard hydration: NaCl 0.45% 1 ml/kg/h 12 hours before and 12 hours after procedure Standard NAc: 2 dd 600 mg, day before and day after procedure.

a mediator of CIN. The study by Merten *et al*. was the first to confirm the efficacy of sodium bicarbonate in clinical practice.[34] They performed an RCT in patients undergoing an elective diagnostic procedure. Patients were randomised to receive a 154 mEq/l infusion of sodium bicarbonate or sodium chloride intravenously, as a bolus of 3 ml/kg/hour for one hour before the administration of contrast, followed by an infusion of 1 ml/kg/hour for six hours after the procedure. These results were confirmed in several recent studies, which differed in study protocol (*table 3*).[35-37] By contrast, a large retrospective study showed that the use of sodium bicarbonate was associated with an increased incidence of CIN. For obvious reasons data of retrospective studies must be interpreted with caution.[38]

The abovementioned studies (summarised in *table 3*) did not compare sodium bicarbonate to standard hydration. The practical advantage of the less time-consuming sodium bicarbonate regimen is evident. Briguori *et al*. compared sodium bicarbonate according the Merten schedule (which provides 630 ml in a 70 kg patient) with the standard hydration regimen of isotonic saline infused at a rate of 1 ml/kg/hour starting 12 hours before and continuing 12 hours after the procedure (equivalent to 1680 ml).[39] In patients with heart failure the infusion rate of isotonic saline was reduced to 0.5 ml/kg/hour. In addition both groups received NAc orally. The incidence of CIN (>25% increase in serum creatinine) was lower in the bicarbonate group than in the saline group (1.9 *vs* 9.9%; p=0.01). These results seem convincing. However, looked at more closely the study poses some questions. First, the differences in hydration volumes between the saline and bicarbonate group were lower than aimed for (1562 ± 585 *vs* 1081 ± 445 ml). Furthermore, in both groups diuresis was more than 1400 ml/day indicating that all patients were well hydrated.

In conclusion: it remains to be proven, especially in volume-depleted patients, that hydration with sodium bicarbonate according to the Merten schedule is a good substitute for standard hydration with isotonic saline. However, in case of emergency procedures when there is not enough time to prehydrate, sodium bicarbonate infusion according to the Merten schedule is probably superior to a short period of saline infusion.

TOXICITY OF GADOLINIUM CONTAINING CONTRAST MEDIA

The risks of contrast-induced nephropathy associated with the use of iodinated contrast media certainly stimulated the application of contrast-enhanced magnetic resonance imaging (MRI) techniques in patients with renal failure. For MRI techniques gadolinium-containing contrast media are used.

Gadolinium is a heavy metal. Gadolinium is very toxic, and free gadolinium causes severe hepatic necrosis. Therefore, the currently used gadolinium containing

Table 3. *Overview of studies with sodium bicarbonate*

Author (year)	$NaHCO_3$ infusion schedule	Comparator	CIN experimental group	CIN control group	Remarks
Merten (2004)[34]	$NaHCO_3$ 154 mmol/l 3 ml/kg/h *1 hour before 1 ml/kg/h *6 hours after	NaCl 154 mmol/l Same infusion schedule	1/60	8/59	Creat 160 µmol/l No hydration No data on volume status of patients
Briguori (2007)[39]	$NaHCO_3$ cf Merten	NaCl 0.9% 1 ml/kg/h -12 to +12 hours	2/108	11/111	Creat 175 µmol/l All patients received NAc 2 dd 1200 mg Expected infusion volume: NaCl 1800 ml, $NaHCO_3$ 675 ml; Diuresis: NaCl 1703 ml, $NaHCO_3$ 1485 ml Actual infusion volume: NaCL 1562 $NaHCO_3$ 1081 ml
Masuda (2007)[35]	$NaHCO_3$ cf Merten	NaCl 0.9% Similar schedule	2/30	10/29	Creat 115 µmol/l
Recio-Mayoral (2007)[37]	$NaHCO_3$ 154 mmol/l, 5 mg/kg iv * 1 hour before + 2400 mg NAc iv	No prehydration	1/56	12/55	Creat 90 µmol/l All patients received posthydration and 2 dd 600 mg NAc after the procedure
Ozcan (2007)[36]	$NaHCO_3$ 154 mmol/l, 1 ml/kg/hour from -6 hour to + 6 hour	NaCl 154 mmol/l, similar schedule	4/88	12/88	Creat 120 µmol/l Third group received 2 dd 600 mg NAc + saline; no effect CIN 11/88

$NaHCO_3$ = sodium bicarbonate; creat = serum creatinine; NaCl = sodium chloride; NAc = N-acetylcysteine.

contrast media are all chelates, which must ensure that no free gadolinium is present in the circulation. Several chelates are available, which differ in structure and ionic strength (*table 4*). Although the chelates bind gadolinium, some free gadolinium will be present and the amount is dependent on the physicochemical properties of the chelate. Non-ionic linear chelates are less stable than ionic macrocyclic chelates.

Initial studies suggested that gadolinium-containing contrast media were relatively safe. These studies only addressed short-term safety.

Over the past years it has become evident that the use of gadolinium-containing contrast media is associated with the development of a severe, life-threatening side effect, i.e. nephrogenic systemic fibrosis, especially in patients with severe renal failure. This entity was initially described in 2000 as nephrogenic fibrosing dermopathy (NFD) by Cowper *et al.* in dialysis patients. NFD is a skin disorder characterised by thickening of the skin, predominantly involving the limbs.[40] Histologically, the skin lesions consist of irregular bundles of collagen, and an increased number of spindled CD34 positive, fibroblast-like cells. There is no evidence of inflammatory cells or eosinophils. In some patients the disorder not only involved the skin, but also the muscles, diaphragm, and organs. In view of the systemic character, the term nephrogenic systemic fibrosis (NSF) was introduced. NSF was not a benign disorder, in many patients the disease progressed to death.[41] In 2006, a relationship between NSF and the use of gadolinium was suggested.[42,43] Grobner described five haemodialysis patients who developed NSF within two to four weeks after administration of gadolinium-DTPA. Another report by Marckman *et al.* described 13 patients with NSF. All patients had severe renal failure; however, five patients were not yet receiving renal replacement therapy. The first sign of NSF was noted 2 to 75 days after exposure to gadodiamide. A recent case-control study included 19 patients with NSF and confirmed the association of NSF with gadolinium exposure.[44] In a multivariate analysis, exposition to gadolinium was the most independent predictor of the development of NSF. In that study, 18 out of 19 cases had been treated with a gadolinium-containing contrast agent, in four of them the interval between exposure and onset of the disease was more than 12 months. Thus far, more than 400 patients with NSF have been reported.[45,46] More than 95% of the evaluated patients had been exposed to gadolinium within three months prior to the onset of disease. The incidence of NSF in patients with end-stage renal disease exposed to gadolinium is estimated at 2 to 5%.[45,47] A recent study suggests that the incidence may be even higher if limited abnormalities of the skin are also considered.[48] Todd *et al.* carefully studied the skin of a cohort of dialysis patients. The skin was evaluated with respect to hyperpigmentation, hardening and thettering. They observed such changes in 16 of 54 (30%) patients exposed to gadopentetate, and in only one of 36 unexposed patients. The presence of these skin lesions was associated with an increased mortality rate, with an adjusted hazard ratio 2.9. Prince *et al.* most recently reported the incidence of NSF using data from two large medical centres.[49] They observed 15 cases of NSF after 83,121 MRI procedures (0.17%). In all patients a linear chelate was used. The incidence was 0.4% in patients on chronic haemodialysis. NSF occurred more frequently in patients with acute renal failure who received Gd-containing contrast media in the phase of deteriorating renal function (incidence 8.4%). In these patients, when haemodialysis was delayed for more than two days, the incidence of NSF amounted to 19% (11 of 58 patients). The exact mechanism of gadolinium-induced skin fibrosis is unknown, although it is suggested that gadolinium may cause changes in fibroblast characteristics. It is not surprising that patients with kidney failure are at increased risk, since the half-life of the gadolinium-containing chelate is increased in patients with renal failure. Although limited data are available, it is likely that also the dose of the contrast agent is an important issue. This was highlighted in the above-mentioned study by Prince *et al.*[49] NSF only occurred in patients who received more than the standard dose of 0.1 mmol/kg. Most reported cases of NSF have been associated with the use of linear gadolinium

Table 4. *Gadolinium-containing contrast media*[45,48]

Name	Trade name	Structure	Charge	Stability	T1/2	Cases with NSF reported to FDA
Gadodiamide	Omniscan	Linear	Non-ionic	14.9	35 sec	283
Gadoversetamide	Optimark	Linear	Non-ionic	15		20
Gadopentetate-dimeglumine	Magnevist	Linear	Ionic	17.7	10 min	125
Gadobenate dimeglumine	MultiHance	Linear	Ionic	16.9		10
Gadoteridol	ProHance	Cyclic	Non-ionic	16.9	3 hours	9
Gadoterate meglumine	Dotarem	Cyclic	Ionic	18.6	>1 month	NA

Stability is conditional stability, expressed in 10 log. Conditional stability is measure of relationship between free Gd and chelate-bound Gd; high values reflect more avid binding. T1/2 reflects the time to release Gd from the chelate. NSF = nephrogenic systemic fibrosis; FDA = Food and Drug Association.

chelates (*table 4*). Until now, no formal case report has documented the occurrence of NSF after the sole use of a macrocyclic chelate, and only one patient has been reported to the FDA's MedWatch.[46] The lower risk associated with the macrocyclic chelate gadoteridol was confirmed in a cohort study, documenting no evidence of NSF in 141 haemodialysis patients after 198 exposures.[50]

Based on the available evidence, it is evident that linear gadolinium chelates should not be used in patients with a GFR <30 ml/min. Although cyclic compounds appear to be safer, additional data are needed to weigh the benefits and risks of the various imaging techniques

CONCLUSIONS

The use of iodinated contrast media is associated with nephrotoxicity, especially in patients with risk factors such as renal failure, vascular disease and diabetes. Risk can be reduced by identification of high-risk patients and proper management, with hydration being the optimal preventive strategy. In case of an emergency procedure, when there is insufficient time to prehydrate, a short infusion protocol with sodium bicarbonate is preferable. There is a lack of evidence to support the use of oral or intravenous N-acetylcysteine or iso-osmolar contrast media.

Nephrogenic systemic fibrosis is a life-threatening complication of the use of gadolinium-containing contrast media in patients with renal insufficiency. Linear gadolinium chelates should not be used in patients with an eGFR <30 ml/min. In patients with eGFR between 10 and 30 ml/min the small chance of NSF with macrocyclic gadolinium-containing chelates must be balanced against the high risk of developing CIN, and the morbidity and mortality associated with the start of dialysis, the use of intravenous catheters etc. In patients without residual renal function the small chance of developing NSF after cyclic Gd-enhanced MRI imaging may tip the balance to the use of iodine containing contrast media. In patients with end-stage renal disease it is advised to perform haemodialysis within three hours after gadolinium administration and repeat this after 24 hours. As the knowledge on Gd-induced toxicity is evolving quickly, it is important to check the literature on this topic regularly. Recent guidelines can be found at www.esur.org.

ACKNOWLEDGEMENT

The authors participated in the guideline committee of the Dutch Institute for Health Care Improvement (CBO). This manuscript is not seen or approved by the members of the committee. The conclusions in this manuscript reflect the opinions of the authors.

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Ten Dam, et al. Toxicity of contrast media.

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

A retrospective analysis of patients treated for superficial vein thrombosis

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ABSTRACT

Introduction: The absolute risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) as well as extension and/or recurrence in superficial vein thrombosis (SVT) of the leg is considerable and underestimated. We retrospectively evaluated therapeutic management, thrombophilic risk factors and clinical outcome of SVT.

Methods: A database search was performed for consecutive patients with a suspected SVT of the lower extremities referred to our institution between 1 January 1999 and 31 December 2004. The primary outcome measure was pain reduction at follow-up. Secondary outcome measures were progression or recurrence of SVT in the leg and the occurrence of (a)symptomatic DVT or symptomatic PE at follow-up.

Results: In 73 patients follow-up information was present (3/76 non-evaluable patients). In 9/32 (28%) of the patients treated with carbasalate calcium, there was progression of SVT as assessed by ultrasonographic evaluation, compared with 3/11 (27%) in the low-molecular-weight heparin (LMWH) group and 3/6 (50%) in the no treatment group. DVT was diagnosed in 5/36 (14%) of the patients treated with carbasalate calcium compared with 1/13 (1%) in the LMWH and 1/3 (33%) in the other treatment groups at follow-up. Furthermore, 34 were tested for thrombophilic defects, 27 of whom had one or more thrombophilic defect.

Conclusion: The results of our study show that SVT may be prone to venous thromboembolism and therefore needs to be treated or carefully followed up.

KEYWORDS

Superficial phlebitis, superficial thrombophlebitis, superficial vein thrombosis, venous thromboembolism, venous thrombosis

INTRODUCTION

The incidence of superficial vein thrombosis (SVT) of the leg has never been adequately assessed, but is estimated to be higher than that of deep vein thrombosis (DVT), which has an incidence of 1 per 1000 inhabitants per year.[1-3] The fact that the incidence is not known can be partially explained by the different terms used for this disease: superficial phlebitis, superficial thrombophlebitis or superficial vein thrombosis. In general 'superficial phlebitis' refers to the clinical findings of inflammation such as pain, tenderness and/or erythema along the affected superficial vein, often palpable as a cord. The term 'superficial vein thrombosis' is used when a thrombus is found by diagnostic testing such as compression ultrasonography (CUS) or phlebography.[4,5]

The absolute risk of DVT or pulmonary embolism (PE) (called venous thromboembolism, VTE) and extension and/or recurrence in SVT is not well known and likely underestimated.[6] Until recently SVT was considered a benign disease, but several studies have suggested otherwise,[7-11] although the association between SVT and VTE has been debated.[12] Because of its location, SVT of the vena saphena magna or the saphenous-femoral junction is thought to have the highest risk of progressing to a deep venous thrombosis and/or embolisation to the pulmonary arteries.[13,14]

Predisposing risk factors for SVT are very similar to those for VTE. These include postoperative states, pregnancy, active malignancies, autoimmune diseases, use of oral contraceptives, previous venous thromboembolism and varicose veins.[15-19] In addition, the factor V Leiden (G1691A) and prothrombin mutation (20210A) as well as deficiencies of the natural anticoagulant proteins C and S are also diagnosed more often in patients with SVT than in healthy individuals, which further strengthens the hypothesis that SVT and VTE have a comparable aetiology.[20-23]

To date patients are often either not treated or receive creams, elastic stockings or non-steroidal anti-inflammatory agents (NSAIDs). The association of VTE with SVT has raised the question whether this conservative management, mainly aimed to improve the painful symptoms, is sufficient. Therefore, several other therapies have been proposed, ranging from surgical ligation or stripping of the affected veins to full-dose anticoagulant therapy.[24-28] After reviewing the available literature on treatment of SVT, active treatment with NSAIDs or LMWH (prophylactically or therapeutically) appears to reduce the incidence of SVT extension and/or recurrence compared with placebo.[6] However, during a longer follow-up this benefit was lost. There is not enough evidence to support surgical intervention or topical treatment based on the literature currently available.[29]

This retrospective follow-up study was performed to evaluate therapeutic management, thrombophilic risk factors and clinical outcome of SVT in our clinic over the past six years. Furthermore, we were interested in the trend of therapeutic management over time in our clinic, since the publication of several therapeutic management studies of SVT. We assessed pain reduction, extension and/or recurrence of SVT in the lower extremities and progression to DVT/PE after treatment.

METHODS

Data collection

The Department of Vascular Medicine of the Academic Medical Center in Amsterdam, the Netherlands, offers a daily diagnostic service for patients who are suspected of having DVT. The ultrasound technicians are specialised in the diagnosis of venous thrombotic disease. Patients visiting this diagnostic service are referred by their general practitioner or are hospitalised for other conditions. Diagnoses of all patients visiting the clinic have been prospectively collected since 1997. In this electronic database a search was performed for patients diagnosed with an SVT of the lower extremities between 1 January 1999 and 31 December 2004. The medical files of all patients were checked for date of onset of symptoms, treatment taken before presentation, date of diagnosis, risk factors for VTE, diagnostic tests used, localisation of the SVT, type of treatment and follow-up information (both history and ultrasound data). Pain and ultrasonographic evaluations were interpreted and scored by two investigators (IW, MH) independently. Extension of an SVT was considered present if the thrombus had extended in length or diameter.

Furthermore, medical files were checked for findings of thrombophilic risk factors (factor V Leiden, prothrombin mutation, deficiency of protein C/S/antithrombin, lupus anticoagulans, anticardiolipin antibodies and elevated levels of factor VIII) and DVT or PE at follow-up. An effort was made to contact patients if follow-up information was missing. Patients identified as having concomitant DVT at the time of diagnosis of SVT were not included. Other exclusion criteria were anticoagulant treatment (except when initiated for the present episode of SVT by their general practitioner), surgical intervention (stripping, ligation or crossectomy) or SVT at another location than the legs.

Outcome measures

The primary outcome measure was pain reduction at follow-up after a minimum of six days to six months. Secondary outcome measures were progression or recurrence of SVT in the leg and the occurrence of (a) symptomatic DVT or symptomatic PE at follow-up after a minimum of six days to six months.

RESULTS

Database search results

The database search for patients with SVT resulted in 131 hits. Of these, 55 patients were excluded from the study for the following reasons: because no SVT was diagnosed (40), SVT was localised in the arm (1), co-existent PE (3) or DVT (4), patients were using anticoagulant treatment for other indications (2), had undergone stripping of the vena saphena magna and/or parva (4), and the medical file could not be retrieved (1). Follow-up information for symptoms and ultrasonographic evaluation was missing in three patients: two women (48 years of age, oral contraceptive use, history of SVT and factor V Leiden and 61 years, no information) and a man (25 years, sickle cell anaemia, a history of venous thrombosis, recent surgery and the prothrombin mutation).

Diagnosis of SVT

The baseline characteristics of the 73 patients are detailed in *table 1*. Patients in whom SVT was diagnosed were relatively young (median 54 years) and there was no difference in sex (47% male). The diagnosis of SVT was confirmed by compression ultrasonography on the day of presentation in 72 of the cases. In one patient the diagnosis of SVT was made by clinical symptoms only at the first visit, but SVT was objectively documented at follow-up. Of the 73 patients SVT was located in the vena saphena magna, the vena saphena parva and in both veins in 38, 20 and 12, respectively. Two of the 73 patients had SVT in a superficial calf vein, in one the location was not described.

Risk factors for SVT: inherited and acquired thrombophilic defects

Table 1 details the risk factors for SVT. In this population, 14 of a total of 57 (21%) patients had a history of VTE. Immobilisation, trauma and surgery preceded a relatively

Table 1. *Baseline characteristics*

	Patients (n=73)	
Characteristic	**n**	**%**
Age (median (years) ± SD)	54 ± 19	
Male gender	34	47
Interval between symptom onset and diagnosis:		
• Median (days)	7	
• Range (days)	1-160	
• ≤14 days	60	86
• Date of onset missing	3	4
Diagnosis confirmed:		
• Complete ultrasound	72	99
• On clinical grounds	1	1
Location superficial vein thrombosis:		
• Vena saphena magna (VSM)	38	52
• Vena saphena parva (VSP)	20	27
• VSM and VSP	12	16
• Superficial calf veins	2	3
• Unclear	1	1
Risk factors (present/absent)	**n/N***	**%**
History of venous thromboembolism	14/43	33
Immobilisation in the last 3 months	5/45	11
Trauma in the last 3 months	6/45	13
Surgery in the last 3 months	4/49	8
Malignancy	3/46	7
Family history of venous thromboembolism	11/36	31
Female risk factors:		
• Oral conceptive use or HRT	9/17	50
• Puerperium (<6 weeks)	4/22	18
• Pregnancy	4/22	18

*Number of patients with risk factors described is variable; HRT = hormonal replacement therapy.

low number of SVTs, i.e. in 5/50 (10%), 6/51 (11%) and 4/53 (8%) patients, respectively. Hormone replacement therapy or oral contraceptives were taken by 9/26 (35%) women with SVT, 4/26 (15%) women were pregnant and 4/26 (15%) were in their puerperium period at the time of diagnosis.

Thirty-four of the 73 patients (47%) were tested for one or more thrombophilic abnormalities. Of the 34 tested patients, 27 (79%) had one or more thrombophilic defect. In 9/31 (29%) of the patients the factor V Leiden mutation was found (1 homozygous). Furthermore, 3/32 (9%) of the patients had a prothrombin mutation: heterozygous (2) and homozygous (1). Two out of 31 patients (6%) had a protein C deficiency and 1/31 patient (0.3%) a protein S deficiency. Elevated factor VIII levels were frequently found (based on a single measurement in the majority of the cases), i.e. 16/25 (64%) patients tested.

Treatment after the established diagnosis of SVT

Treatment prior to referral

In 12 of the 73 cases the patient had been treated before referral, with antibiotics (6), vitamin K antagonists (2), elastic compression stockings and carbasalate calcium (1), carbasalate calcium alone (1), prophylactic dose of low-molecular-weight heparin in a hospitalised patient (1) and hiroid cream (1).

Following the established diagnosis of SVT, 40 of the 73 (55%) patients received treatment with carbasalate calcium (500 to 600 mg three times daily) for a median duration of ten days (range 3 to 21; one missing value) (*table 3*). Two of these patients were also given an elastic compression stocking. Fifteen patients (21%) were treated with a therapeutic dose of low-molecular-weight heparin for a median duration of 14 days (range 7 to 64), two patients also got a prescription for an elastic compression stocking (ECS), one of whom also received antibiotics. Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed to three patients (4%) as were vitamin K antagonists. In one patient (1%) low-molecular-weight heparin was combined with carbasalate calcium for treatment of the SVT. Six patients (8%) received no medical treatment or compression stockings.

Carbasalate calcium was predominantly given as treatment for SVT between 1999 and 2003. In 2004, however, more patients were treated with low-molecular-weight heparin.

Clinical outcome

Reduction of symptoms at follow-up

Most patients (n=60, 87%) were referred within two weeks after the onset of symptoms (median 7 days; range 1 to 160; three missing). Twenty-three patients out of 36 (64%) treated with carbasalate calcium compared with 12/12 (100%) in the low-molecular-weight heparin group and 1/4 (25%) in the no treatment group reported reduction in pain at follow-up (*table 2*). Another two patients had a reduction in symptoms after treatment with low-molecular-weight heparin, which was prescribed when pain persisted after an initial treatment with carbasalate calcium and no treatment. Increase in pain was observed in 5/36 (14%) of the patients treated with carbasalate calcium. No patients had increased pain after treatment with low-molecular-weight heparin and 1/4 (25%) after not being treated. Data on symptoms were missing in 11/73 (15%) of the patients, four of whom had an SVT progression or recurrence and two had a DVT at follow-up.

Progression and/or recurrence of SVT at follow-up

Ultrasonographic evaluation of SVT at follow-up was available in 56/73 patients (77%) (median 11 days after diagnosis of SVT; range 5 to 129). In 9/32 (28%) of the patients treated with carbasalate calcium there was progression and/or recurrence of SVT as assessed by ultrasonographic evaluation, compared with 3/11 (27%) in the low-molecular-weight heparin and 3/6 (50%) in the no treatment group (*table 2*). Nine of 17 patients with missing results on ultrasonographic evaluation of SVT reported pain reduction

Table 2. *Symptoms at follow-up after treatment with carbasalate calcium, nadroparin or other treatments*

	Pain			
Treatment (n*)	**Increase (n, %)**	**Same (n, %)**	**Decrease (n, %)**	**Unknown (n)**
Carbasalate calcium (36)	5, 14	8, 22	23, 64	4
Nadroparin (12)	0, -	0, -	12, 100	3
No treatment (4)	1, 25	2, 50	1, 25	2
Vitamin K antagonists (3)	0, -	0, -	3, 100	0
NSAIDs (3)	1, 33	0, -	2, 67	0
Nadroparin + carbasalate calcium (1)	0, -	0, -	1, 100	0
Other (3)	1, 33	0, -	2, 67	2

*Missing follow-up information (see column 'unknown') was not included in the total number of treated patients.

Table 3. *Superficial venous thrombosis and deep venous thrombosis at first follow-up after treatment with carbasalate calcium, nadroparin or other treatments*

	Results compression ultrasonography					
Treatment (n*)	**Extension and/or recurrence of superficial venous thrombosis**			**Deep venous thrombosis**		
	Yes (n, %)	**No (n, %)**	**Unknown (n)**	**Yes (n, %)**	**No (n, %)**	**Unknown (n)**
Carbasalate calcium (32 *vs* 36)	9, 28	23, 72	8	5, 14	31, 86	4
Nadroparin (11 *vs* 13)	3, 27	8, 73	4	1, 8	12, 92	2
No treatment (6)	3, 50	3, 50	0	0, -	6, 100	0
Non-steroidal anti-inflammatory drugs (3)	1, 33	2, 67	0	0, -	3, 100	0
Vitamin K antagonists (2 *vs* 3)	0, -	2, 100	1	0, -	3, 100	0
Nadroparin + carbasalate calcium (1)	1, 100	0, -	0	0, -	1, 100	0
Other (1 *vs* 3)	0, -	1, 100	4	1†, 33	2, 67	2

*Missing follow-up information (see column 'unknown') was not included in the total number of treated patients. †Patient was treated with hiroid cream

at follow-up, two patients had a DVT and six patients did not have a symptomatic VTE at follow-up. Eight of 17 patients had no ultrasonographic evaluation of SVT and DVT at follow-up, five had a reduction in symptoms at follow-up and seven did not have a symptomatic VTE at follow-up.

Occurrence of DVT at follow-up

Ultrasonographic evaluation of DVT at follow-up was available in 65/73 (89%) of the patients (median 10 days after diagnosis of SVT; range 3 to 129). Two patients developed a DVT within one week (day 3 and 5). DVT was diagnosed in 5/36 (14%) of the patients treated with carbasalate calcium compared with 1/13 (8%) in the low-molecular-weight heparin and 1/3 (33%) in the other treatment group at follow-up (*table 3*). As mentioned above, of the eight patients without ultrasonographic evaluation, five had a reduction in symptoms at follow-up and seven did not have symptomatic VTE at follow-up.

DISCUSSION AND CONCLUSION

In our centre, SVT was traditionally treated with carbasalate calcium, because of its anti-inflammatory and pain-reducing properties. In 2004, an increasing number of patients with SVT were treated with low-molecular-weight heparin, which was probably due to the publication of randomised trials on treatment and natural history of SVT, showing that active treatment with NSAIDs or LMWH may reduce the incidence of progression and/or recurrence of SVT.[27,30] Another reason for abandoning treatment with carbasalate calcium was the lack of evidence for the efficacy of this type of treatment for SVT.

Our findings indicate that SVT has similar inherited and acquired risk factors to those known for VTE, as has been described by others.[19,20,23]

Nevertheless, SVT progressed to DVT in 7/65 (11%) of the cases, which confirms that SVT is not a benign disease.[6,10,31] Interestingly, pain reduction at follow-up was accomplished more often in patients treated with low-molecular-weight heparin compared with treatment with carbasalate calcium. SVT progression and/or recurrence was comparable in both the carbasalate calcium and low-molecular-weight heparin group, but higher in patients who were not treated at all. DVT occurred in one patient treated with low-molecular-weight heparin compared with five patients in the carbasalate calcium group. None of the patients who had been managed conservatively developed DVT. These findings should be interpreted with caution, since the interventions were not prescribed in a randomised fashion,

and the observations are likely to be biased by selective treatment of patients with more severe symptoms.

Risk factors for VTE are also found in patients with SVT, which strengthens the concept that SVT and VTE share the same aetiology. The results of our study show that patients with SVT may be prone to VTE and therefore need to be treated or carefully followed. Furthermore, these results stress the need for large (multi-centre) trials for the treatment of SVT.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Changes of bone mineral density, quantitative ultrasound parameters and markers of bone turnover during treatment of hyperthyroidism

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ABSTRACT

Background: The extent of reversibility of loss of bone mass density (BMD) in hyperthyroid patients after treatment is not clear.

Methods: The bone density measured by dual X-ray absorptiometry (DXA), the parameters of quantitative ultrasound (QUS) and biochemical markers of bone turnover of 22 patients were measured before and after one year of treatment with thiamazole and levothyroxine.

Results: The mean BMD of lumbar spine, femoral neck, Ward triangle and total hip bone density increased by 5.9, 3.8, 3.0 and 6.7%, respectively, after one year of treatment, all significant increases except the increase in Ward triangle bone mass density. There was no significant change in QUS parameters, although the increase in broadband ultrasound attenuation (BUA) of the left and right calcaneus of 5.2 and 4.2%, respectively, suggests reversibility in the long term. Urinary pyridinoline cross-links declined significantly and normalised after treatment. Bone-specific alkaline phosphatase declined after an initial rise, not (yet) reaching normal values after one year of treatment.

Conclusion: The decline in BMD in hyperthyroid patients measured by DXA seems to be reversible after treatment of hyperthyroidism, whereas a change in the QUS parameters, probably also an indicator of bone elasticity and architecture, could not be found.

KEYWORDS

Bone mass, hyperthyroidism, quantitative ultrasound

INTRODUCTION

Hyperthyroidism is associated with osteoporosis. Von Recklinghausen was the first to describe the fractures and the 'worm eaten' appearance of the bones of patients suffering from hyperthyroidism.[1] These days there are therapeutic options such as antithyroid drugs and radioiodine, yet there is still a reduction in bone density in hyperthyroid patients and in patients with subclinical hyperthyroidism by endogenous overproduction or oversuppletion of thyroid hormone.[2] The reason for this is the direct stimulating effect of the thyroid hormone[3] and possibly also the negative regulating effect of thyroid-stimulating hormone (TSH)[4] on bone resorption. Also, increased serum interleukin-6 concentrations in hyperthyroid patients favour osteoclast production and may be an effector of the action of parathyroid hormone on bone.[5]

The extent of reversibility of bone loss after the start of treatment is unclear. Previous studies have yielded variable results. Some studies showed complete normalisation of the bone density.[6-9] Other studies reported no or incomplete recovery of bone density after treatment.[10-16]

Dual X-ray absorptiometry (DXA) is currently the most frequently used instrument for measuring bone mass density (BMD). With little radiation it gives very precise and accurate measurements. There is a strong relationship between fracture risk and BMD measured by DXA.[17]

Quantitative ultrasound (QUS) has also proven to be a good predictor of fracture risk.[18] Instead of measuring bone density directly, it measures the transmission of ultrasound through accessible limb bones or the reflectance of the ultrasound waves from the bone surface. QUS might provide information not only on bone mass but also on bone elasticity and structure.[19-21] Advantages are the lower expense,

portability, and lack of radiation exposure. Yet, the criteria for diagnosing osteoporosis are not well established.
Biochemical markers of bone turnover, such as pyridinoline cross-links and bone-specific alkaline phosphatase, are increased in hyperthyroidism suggesting an increase in osteoclastic and osteoblastic activity. Previous studies show that these markers normalise after treatment.[22-24]
The aim of this study was to determine the influence of treatment of hyperthyroid patients on the bone density measured by DXA, on the parameters of QUS and the effect on the biochemical markers of bone turnover.

SUBJECTS AND METHODS

Subjects

Twenty-two consecutive patients with untreated thyrotoxicosis, caused by Graves' disease, attending our outpatient department were enrolled. Eighteen women and four men participated in the study and gave informed consent. The inclusion criteria were:

- clinical symptoms of hyperthyroidism;
- a suppressed serum thyroid-stimulating hormone (TSH <0.04 mU/l) and an elevated serum free T4 (FT4 >25 pmol/l) and/or free T3 (FT3 >7 pmol/l) and
- confirmation of the Graves hyperthyroidism by Tc99 scan.

Patients with comorbidity (hypo- and hyper-parathyroidism, vitamin D deficiency, Cushing's disease, inflammatory bowel disease, malabsorptive diseases) or on medication (steroids, bisphosphonates, calcium, vitamin D, or hormonal replacement therapy) influencing bone turnover were excluded. Also patients postmenopausal for less than five years were excluded.
All patients were treated with thiamazole and levothyroxine according to the block and replace regime in order to obtain and maintain euthyroid status. Patients were treated with thiamazole 30 mg once a day as monotherapy for six weeks, and consecutively levothyroxine was added six weeks later, depending on results of the TSH levels.

Methods

Serum thyroid hormones, TSH, calcium (normal value 2.15 to 2.55 mmol/l) and phosphate (normal value 0.8 to 1.5 mmol/l) were measured at baseline and after three, six and 12 months. TSH was measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay (IMMULITE Third-generation TSH, Diagnostic Products Corporation, Los Angeles USA, normal value 0.4 to 4.0 mU/l). The FT4 and FT3 concentrations were measured with a solid-phase immunometric assay (IMMULITE Free T4 and Free T3, normal values 10 to 24 pmol/l and 2.7 to 7.0 pmol/l, respectively).
All patients underwent a ^{99m}Technetium scan with 110 MBq Technetium and were scanned with a gamma camera with an energy level of 110 keV. All patients showed a pattern comparable with autoimmune hyperthyroidism.
The biochemical markers of bone turnover, bone-specific alkaline phosphatase (Metra kit, Quidel, USA) and urinary pyridinoline cross-links (sCTx Elecsys Roche), were measured at baseline and after three, six, nine and 12 months. Because of the sex- and age-related variability of bone turnover parameters, results were expressed as Z scores, subtracting the mean value of an age-, ethnicity-, and sex-matched reference population from the patient's value and dividing the difference by the standard deviation (SD) of the reference population. A normal Z score was considered to be between -2 and 2.
Autoantibodies to the TSH receptor (RRA Brahms, normal value <35 kU/l) and anti-TPO antibodies (Immulite 2000 Siemens, normal value <14 E/l) were determined at baseline.
DXA measurement and quantitative ultrasound were performed at baseline and after 12 months. DXA measurement (Hologic QDR 2000, Bedford MA, USA) was performed at the lumbar spine (L1 to L4) and left femur (femoral neck, Ward triangle, and total hip). BMD was expressed in g/cm^2. The Z score was calculated by subtracting the mean BMD of an age-, ethnicity-, and sex-matched reference population from the patient's BMD and dividing the difference by the SD of the reference population.
Quantitative ultrasound was performed with a Hologic ultrasound (Sahara, Hologic Inc, Bedford MA, USA) at os calcis on the left and right side with two subsequent measurements each. Afterwards the mean value of each side was calculated. The QUS device measured the broadband ultrasound attenuation (BUA, dB/MHz) and speed of sound (SOS, m/s).
DXA measurements were performed by independent analists, who were not involved with the study. The Ethics Committee of Máxima Medical Centre gave permission for the study.

Statistical evaluation

Results were expressed as the mean and SD. Data before and after treatment were analysed by paired Students T-test, after assessing the normal distribution of the data by Stem-and-Leaf plot. If this was not normally distributed, the Wilcoxon ranking test was applied. A p value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 40 years, range 24 to 62 years; 82% of the patients were female. The mean body mass index (kg/m^2) was 23.6 with a range of 18.0 to 30.6 kg/m^2.

Seven patients were postmenopausal with a mean age of 57 years.

Table 1 shows the levels of serum thyroid hormones and biochemical markers at baseline, three, six and 12 months. Thyroid hormones decreased and TSH levels rose during treatment and generally reached a normal range. In two of the patients, the levels of FT4 had not yet reached the normal value, despite 12 months of treatment. Mean serum calcium and phosphate decreased but were within normal ranges throughout the study. Serum calcium decreased significantly from 2.36 mmol/l (SD 0.09) to 2.26 mmol/l (SD 0.09), a decrement of 0.10 mmol/l (SD 0.09) after 12 months of treatment.

Anti-TPO antibodies were found in 64% of the patients. Autoantibodies to the TSH receptor were also positive in 64% of the patients.

In *figure 1* the mean values of the Z score of bone-specific alkaline phosphatase and urinary pyridinoline cross-links during one year of treatment of hyperthyroidism are shown. Mean serum bone-specific alkaline phosphatase was above normal level at baseline (Z score 2.5 ± 2.5). After an initial rise to a Z score of 7.3 after three months, bone-specific alkaline phosphatase declined, but did not reach the normal range (Z score 2.9 ± 3.2). Urinary pyridinoline cross-links were above normal values at baseline (Z score 6.0 ± 5.0), but declined significantly ($p<0.01$) after treatment and reached normal range (Z score 0.3 ± 1.8).

The results of the DXA measurements are shown in *table 2* and *figure 2*. At baseline the mean Z scores of the bone density of femoral neck, total hip, inter and trochanter major were <0. After treatment all mean Z scores were >0. The BMD of lumbar spine, femoral neck, ward triangle and total hip all increased after 12 months of treatment. The mean lumbar spine BMD increased from an initial value of 1.01 g/cm² to 1.07 g/cm², an increase of 5.9% after one year of treatment. Femoral neck, Ward triangle and total hip bone density increased by 3.8, 3.0 and 6.7%, respectively, after one year of treatment. Only the increase of the Ward triangle BMD was not significant.

Figure 1. *Mean Z score of the bone turnover parameters bone-specific alkaline phosphatase and pyridinoline cross-links during one year of treatment with thiamazole and levothyroxine*

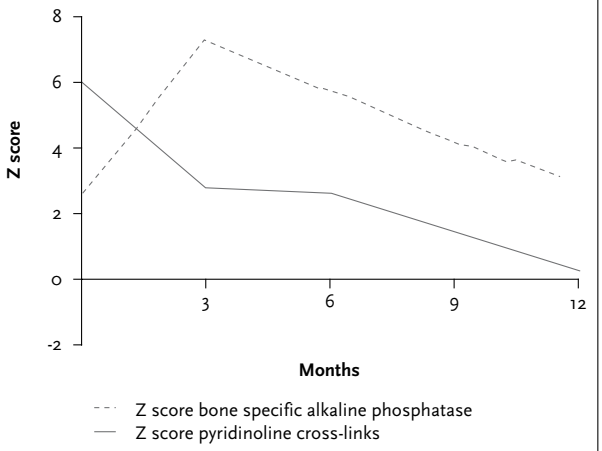
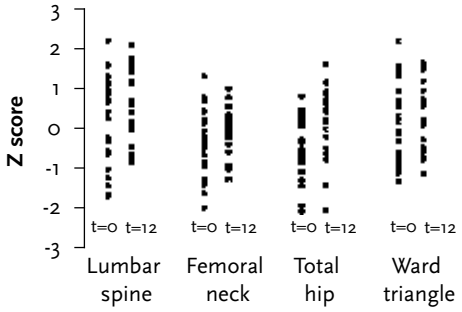


Figure 2. *Z scores of the bone mass density of the individual patients measured by DXA at lumbar spine, femoral neck, total hip and Ward triangle before and after 12 months of treatment with thiamazole and levothyroxine*



t=0 = z score before treatment; t=12 = z score after 12 months of treatment.

Table 1. *Serum thyroid hormone levels and biochemical markers calcium and phosphate (mean ± SD)*

Serum level (normal value)	Baseline	3 months	6 months	12 months	P value (difference 12 months-baseline)
TSH (0.4-4.0 mU/l)	0.0032 ± 0.01	0.38 ± 0.88	2.05 ± 2.94	3,.1 ± 3.76	-
FT4 (10-24 pmol/l)	54.2 ± 17.9	22.5 ± 10.3	20.36 ± 12.49	18,8 ± 5.17	-
FT3 (2.7-7.0 pmol/l)	15.2 ± 6.5	6.23 ± 4.26	5.45 ± 3.52	4.29 ± 1.33	-
Calcium (2.15-2.55 mmol/l)	2.36 ± 0.09	2.30 ± 0.07	2.27 ± 0.07	2.26 ± 0.09	0.000
Phosphate (0.8-1.5 mmol/l)	1.26 ± 0.28	1.13 ± 0.22	1.18 ± 0.18	1.15 ± 0.14	0.085

TSH = thyroid-stimulating hormone; FT = free thyroid.
Measured at baseline and after three, six and 12 months during treatment of hyperthyroidism with thiamazole and levothyroxine according block and replace regime.

Table 2. *Mean values ± SD of DXA measurements BMD (g/cm²) and Z score*

	Baseline BMD (g/cm²)	12 months BMD (g/cm²)	P value BMD	Baseline Z score	12 months Z score	P value Z score
Lumbar spine	1.01 ± 1.4	1.07 ± 0.11	0.003	0.12 ± 1.10	0.63 ± 0.89	0.001
Femoral neck	0.80 ± 0.10	0.83 ± 0.08	0.028	-0.25 ± 0.84	0.04 ± 0.62	0.004
Total hip	0.89 ± 0.10	0.95 ± 0.10	0.000	-0.34 ± 0.82	0.17 ± 0.89	0.000
Ward triangle	0.67 ± 0.15	0.69 ± 0.12	0.552	0.19 ± 0.98	0.29 ± 0.86	0.42

The mean BUA measured by a QUS device at the left and right calcaneus increased by 5.2 and 4.2% after 12 months, but this increase was not significant (*table 3*). The SOS barely increased after 12 months; left and right 0.07 and 0.03%, respectively. There was no significant change.

DISCUSSION

Our study shows that BMD of patients with hyperthyroidism measured by DXA increases during the first year of treatment with thiamazole and levothyroxine. The mean BMD of lumbar spine, femoral neck and total hip all increased significantly by 5.9, 3.8 and 6.7%, respectively.

Previous studies reported varying percentages of increment. Only Toh and colleagues found no significant difference in two years of treatment after a significant decrease in bone mineral content (BMC) in the first year and a recovery in the second year, using a single-photon absorptiometry. Krolner and colleagues found an increase of lumbar spine BMC of 3.7% using dual-photon absorptiometry. Diamond *et al.* reported a significant increase of 6.6% of lumbar spine BMD in one year, measured by DXA. Femoral neck and trochanter did not change significantly (increment 1.2 and 3.2%, respectively). A recent study by Acotto and colleagues showed a large increase of 10.4% of lumbar spine BMD and 8% of femoral neck BMD after one year of treatment and 14 and 12.2%, respectively, after two years of treatment, measured by DXA. Rosen *et al.* suggested a longer lasting effect on bone mineral density by reporting an increase of lumbar spine BMD of 11% after five years of treatment. Karga *et al.* found no significant difference in Z score after three years of treatment in comparison with controls. Langdahl and colleagues also found a normal bone quantity (mineral content and density) in hyperthyroid patients, after treatment for at least four years. After performing a meta-analysis, Vestergaard *et al.* found a decreased bone mineral density and an increased fracture risk in hyperthyroid patients, with normalisation of bone density after one to four years of treatment.

However, whether the damage of the architecture and elasticity (quality) of the bone due to a period of hyperthyroidism is reversible after treatment is not well known. *In vitro* studies suggest that quantitative ultrasound not only provides information on bone density but also on bone architecture and elasticity. Acotto *et al.* reported significantly lower QUS parameters (BUA and SOS) in hyperthyroid patients in comparison with controls.[25] Not many studies have investigated changes in QUS parameters of the calcaneus in treated hyperthyroid patients.
Acotto *et al.* recently reported an increase in mean BUA of 5.4% after one year but then a decrease of 1.6% after two years of treatment. SOS increased by 1.2% after two years. However, ultrasound parameters did not reach normal values after two years of treatment. Our study could not confirm these results: we found no change in mean SOS (increase of 0.07 and 0.03% on left and right calcaneus) during the first year of treatment. Although BUA increased by 5.4 and 4.2% on the left and right side, respectively, these changes were not statistically significant. A new study, including more patients and with a longer follow-up, is needed to confirm the suggested increase of BUA and determine the reversibility in the long term. For practical use the development of quality standards for and cross-calibrations of QUS as well as criteria for diagnosing osteoporosis are necessary.

Several studies reported increased markers of bone turnover in hyperthyroid patients.[15,21-23] Our study shows comparable results: after treatment of hyperthyroidism urinary pyridinoline cross-links, a marker of bone

Table 3. *Mean values of broadband ultrasound attenuation (BUA) and speed of sound (SOS) at baseline and after 12 months of treatment*

	Mean ± SD at baseline		Mean ±SD after 12 months		P value	
	Left	Right	Left	Right	Left	Right
BUA (dB/MHz)	72.6 ± 15.5	72.7 ±15.7	76.4 ± 14.8	75.8 ± 14.1	0.110	0.180
SOS (m/s)	1543.0 ± 32.5	1542.3 ± 30.5	1544.1 ± 31.3	1542.7 ± 32.8	0.728	0.777

resorption, declines rapidly and normalises. Bone-specific alkaline phosphatase, a marker of bone formation, declines after an initial rise during the first three months of treatment, not (yet) reaching normal values after one year of treatment.

CONCLUSION

Our study shows a significant increment in BMD measured by DXA after one year of treatment. The QUS parameters, an indicator not only of bone density but probably also of bone architecture and elasticity, did not change significantly. More studies with long-term follow-up and larger patient populations have to be performed to assess the reversibility of declined QUS parameters as indicator of bone architecture and elasticity in hyperthyroid patients during treatment. The increased markers of bone turnover declined during treatment. This result is consistent with results of previous studies.

ACKNOWLEDGEMENTS

We thank MSD for providing the quantitative ultrasound device, Eveline van der Veer for measurement of markers of bone turnover and Professor A. Hermus for discussing the article with us.

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CASE REPORT

Acute refractory hyperkalaemia and fatal cardiac arrest related to administration of liposomal amphotericin B

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ABSTRACT

A 36-year-old male with acute myeloid leukaemia was treated with liposomal amphotericin B for a breakthrough fungal infection with *Absidia corymbifera* during voriconazole and caspofungin therapy for invasive pulmonary aspergillosis.

Four episodes of hyperkalaemia developed with a highly probable relation to infusion of liposomal amphotericin B, of which the last episode was characterised by severe, refractory hyperkalaemia and fatal cardiac arrest. The available literature on severe hyperkalaemia and cardiac arrest during administration of both conventional and liposomal amphotericin B is reviewed here and revealed only four similar cases. The most likely mechanism of toxicity is the release of potassium from a variety of mammal cells including erythrocytes and endothelial cells. Whether prevention of toxicity can be established by decreasing the infusion rate is unclear but conceivable.

KEYWORDS

Cardiac arrest, fungal infection, hyperkalaemia, liposomal amphotericin B

INTRODUCTION

Although voriconazole is now standard empiric antifungal therapy for opportunistic fungal infections,[1] conventional amphotericin B deoxycholate (C-AmB) is still recommended for certain clinical conditions, for instance when (breakthrough) infections with azole-insusceptible moulds or yeasts occur or when intolerance for azoles is present. However, an important limitation for the use of C-AmB is the appearance of hazardous side effects. In particular, administration of higher doses of C-AmB may be nephrotoxic and may lead to renal failure and severe electrolyte disturbances (hypokalaemia, hypomagnesaemia).[2] Aggravating infusion-related reactions have been documented as well, including fever, rigors, chills, myalgias, arthralgias, nausea, vomiting, headache and bronchospasms.[2] The introduction of lipid formulations of AmB (L-AmB) reduced nephrotoxicity and infusion-related side effects, which made L-AmB an attractive alternative for patients at risk for renal failure or C-AmB intolerance. However, a rare and less-documented side effect of both C-AmB and L-AmB is the potential for the development of acute severe hyperkalaemia related to its administration. Here, we describe a patient who developed a breakthrough fungal infection with *Absidia corymbifera* (a nonseptate mould related to the class of zygomycetes) during antifungal therapy with voriconazole and caspofungin for invasive pulmonary aspergillosis. Treatment with L-AmB was initiated, which ultimately resulted in a fatal cardiac arrest due to acute refractory hyperkalaemia on the 24th day of treatment with L-AmB.

CASE REPORT

A 36-year-old male was diagnosed with acute myeloid leukaemia (AML) requiring cytostatic therapy. During induction chemotherapy, the patient developed neutropenic fever caused by pneumonia of the right upper lobe and treatment with broad-spectrum antibiotics (imipenem-cilastatin) was initiated. After three days, the fever persisted

and empiric antifungal therapy with voriconazole was started. Despite this regime, his clinical condition did not improve and neutropenia persisted. Therefore, early allogenic haemopoeitic stem cell transplantation was scheduled. Unfortunately, respiratory failure developed shortly after transplantation and the patient was transferred to the intensive care unit for mechanical ventilation. A bronchoscopy was performed showing white viscous plugs very suggestive of fungal infection. Bronchoalveolar lavage fluid showed a positive calcofluor together with a positive serum galactomannan antigen test, indicative for invasive pulmonary aspergillosis. Because the galactomannan antigen test showed an increased titre during voriconazole therapy, caspofungin was added. Despite this combination therapy, the patient's respiratory condition deteriorated slowly in the presence of a persistent consolidation of the upper lobe of the right lung. A lobectomy of the right upper lung was performed showing histopathological evidence of invasive fungal infection with visualisation of septate hyphae, massive inflammation and necrosis. Furthermore, a positive polymerase chain reaction for *Absidia corymbifera* was isolated from pleural effusion and liposomal amphotericin B was initiated subsequently (5 mg/kg administered over two hours). On the 24th day of treatment with L-AmB, acute cardiac arrhythmias developed just after the L-AmB infusion was ended, resulting in ventricular fibrillation and cardiac resuscitation was started. Blood samples taken at the onset of cardiac arrest demonstrated a plasma potassium level of 9.2 mmol/l. Repetitive administration of bicarbonate and insulin/glucose did not decrease the potassium level and despite administration of calcium gluconate and multiple attempts at electric defibrillation, the cardiac arrhythmias persisted and further resuscitation was withheld. Autopsy showed no evidence of coronary artery disease or myocarditis. Massive fungal invasion was demonstrated in both lungs, thyroid gland, liver and spleen.

Examining this case carefully after this unexpected death, we found three previous episodes of sudden hyperkalaemia: on day 9, 10 and 11 of L-AmB therapy, plasma potassium levels were also increased at the end of L-AmB infusion (*table 1*). On two of these episodes short-term sinus bradycardia (40 beats/min) occurred which resolved after correction of the plasma potassium level with glucose/

Table 1. *Laboratory results prior, during and after L-AmB infusion (5 mg/kg)*

pH	**Day 9**	**Day 10**	**Day 11**	**Day 24***	**Units**	**Reference**
18.00	7.40	7.42	7.32	7.40		7.35-7.45
22.00	7.40	7.24	7.30	7.17		
23.00	NA	7.31	7.18	7.30		
Bicarbonate						
18.00	23.2	24.7	23.3	32.5	mmol/l	22-28
22.00	23.7	21.1	21.4	27.0		
23.00	NA	22.6	20.9	34.5		
Sodium						
18.00	131	131	126	135	mmol/l	136-145
Potassium						
18.00	3.4	4.7	4.9	4.2	mmol/l	3.5-4.9
22.00	4.7	6.1	6.9	8.9		
23.00	NA	4.6	7.0	9.2		
Creatinine						
18.00	80	93	115	83	µmol/l	60-110
23.00	NA	111	NA	NA		
Creatine kinase						
18.00	NA	NA	31	8	U/l	<170
23.00	NA	39	NA	NA		
Glucose						
18.00	6.6	7.2	6.4	7.1	mmo/l	3.8-8.0
23.00	5.4	14.4	17.8	12.1		
Calcium ionised						
18.00	1.10	1.07	1.08	1.06	mmol/l	1.10-1.30
23.00	1.10	1.00	1.21	1.74		
Event	None	Sinus bradycardia	Sinus bradycardia	Ventricular fibrillation		
Intervention	None	Glucose/insulin	Glucose/insulin Calcium gluconate	Sodium bicarbonate Calcium gluconate		

Infusion was started at 20.00 hrs and completed at 22.00 hrs. *Glucose/insulin was also given. NA = not available.

insulin. Renal function deteriorated during this period, demonstrated by an increase in serum creatinine, but recovered within a few days while L-AmB was continued. Why the patient developed refractory hyperkalaemia on the 24th day of treatment remains unclear; renal function had recovered to within normal limits, and there were no signs of rhabdomyolysis, haemolysis or severe acidosis. Also no medication errors could be identified and the infusion rate of L-AmB was unchanged (375 mg, dissolved in 200 ml dextrose 5% administered in two hours). On the other hand, our patient was being treated with many drugs that may induce hyperkalaemia, including ciclosporin, mycophenolate mophetil, propofol, nadroparin and cotrimoxazole; however, there seemed to be a highly probable time-relationship between the administration time of L-AmB and the occurrence of hyperkalaemia.

DISCUSSION

Reviewing the literature, we identified four previous well-documented cases of acute, severe hyperkalaemia and cardiac arrest in relation to administration of either C-AmB or L-AmB (*table 2*). Craven described a case of repeated acute hyperkalaemia and ventricular fibrillation after a single dose of 1.4 mg/kg C-AmB administered in 45 minutes in an anuric patient a few hours prior to haemodialysis.[3] Laboratory results revealed no evidence of progressive haemolysis or rhabdomyolysis. This author noted that in two other patients, prolonged infusion (four hours) during haemodialysis demonstrated lower peak concentrations of C-AmB without development of hyperkalaemia. Burke *et al.* described a case in which L-AmB (5 mg/kg) was prescribed for cryptococcal meningitis.[4] However, C-AmB in the same dosage was administrated mistakenly on two consecutive days. This overdose resulted in cardiac arrhythmias, severe hyperkalaemia, haemolysis and acute renal failure. A similar medication error with an overdose of C-AmB resulting in severe hyperkalaemia, cardiac arrest and death has been described previously.[5] Barcia described a child with a disseminated candida infection who developed acute hyperkalaemia during infusion of L-AmB (5.0 mg/kg over one hour) accompanied with cardiac arrhythmias.[6] During resuscitation laboratory results demonstrated a potassium level of 16.0 mmol/l without signs of haemolysis or rhabdomyolysis.

Pathogenesis

Conventional amphotericin B deoxycholate (C-AmB) is a natural product of *Streptomyces nodosus* and works by selective binding with ergosterols of the fungal membrane thereby forming channels into the cell membrane. Formation of these channels will increase cell permeability and may lead to efflux of cellular potassium and other intracellular components, resulting in metabolic disruption, osmotic imbalance and cell death. The selectivity of C-AmB action is due to its 8.5-fold higher affinity for the ergosterol component of fungal cell membranes than for cholesterol, which is the predominant sterol found in mammalian membranes. However, C-AmB may also interact with cholesterol-containing human cell membranes, which in turn may result in cellular injury and end-organ dysfunction. This cellular injury has been illustrated

Table 2. *Case reports of severe hyperkalaemia and cardiac arrhythmias related to administration of liposomal amphotericin B (L-AmB) or conventional amphotericin B (C-AmB)*

Author, year	Diagnosis	Sex	Age	Therapy	Dose mg/kg	Infusion time	Day of therapy	Potassium (mmol/l)	Cardiac event	Outcome
Groot, 2008	Acute myeloid leukaemia Invasive pulmonary aspergillosis + zygomycosis	M	36	L-AmB	5.0	2 hours	24	9.2	Cardiac arrest	Death
Burke, 2006	SLE nephritis Cryptococcal meningitis	F	41	C-AmB	5.0 AOD	2 hours	3 4	9.5 9.1	VT VT	Death on day 6 from MOF
Barcia, 1998	Acute lymphoblastic leukaemia Disseminated candida infection	M	4	L-AmB	5.0	1 hour	3	16.0	Cardiac arrest	Death
Cleary, 1993	Histiocytosis + severe organ involvement + unconfirmed Candida fungaemia	F	7	C-AmB	5.0 AOD	2 hours	3	12.2	Cardiac arrest	Death
Craven, 1985	SLE nephritis Cryptococcal endophthalmitis	F	19	C-AmB	1.4	45 minutes	15 16	8.4 9.1	VF VF	Death day 53 from progressive disease

SLE = systemic lupus erythematosus; M = male; F = female; AOD = accidental overdose; VT = ventricular tachycardia; VF = ventricular fibrillation; ECG = electrocardiogram.

in animal studies, and demonstrated that high plasma concentrations and rapid infusions of C-AmB resulted in acute hyperkalaemia and haemolysis.[7,8] Doses between 5 and 15 mg/kg of C-AmB over 15 seconds to 5 minutes caused severe hyperkalaemia and consequently ventricular arrhythmias which were lethal within 15 minutes.[8] The authors found little evidence of haemolysis and suggested potassium efflux from other cells than red blood cells. This was confirmed by others who demonstrated an increased permeability of endothelial cells after C-AmB administration resulting in massive cellular potassium efflux.[9]

These findings do raise the question what the infusion rate of AmB should be. Clinical studies regarding the relationship between the infusion rate of C-AmB and toxic effects show varying results. Ellis *et al.* compared an infusion rate of 45 minutes *vs* four hours in a large cohort and found higher toxicity in the rapid infusion group.[10] Increased toxicity consisted of chills, tachycardia, nausea and vomiting. They did not report any cases of elevated potassium concentrations or cardiac arrhythmias in any of the treatment groups. On the other hand, other investigators concluded that rapid infusion of C-AmB within one hour was safe and did not increase toxicity.[11-13] Whether the toxicity of lipid formulations of AmB depends on the infusion rate is unclear. In one animal study with rabbits, a single dose of 1.5 mg/kg C-AmB administered in five minutes was lethal due to cardiac toxicity while doses up to 10 mg/kg of L-AmB administered within the same time were tolerated well.[14] Clinical trials comparing different infusion rate strategies of L-AmB are lacking.

Treatment and prevention

In general, treatment of AmB-related acute cardiac toxicity is aimed at the correction of the increased plasma potassium level. Cardiac toxicity can be antagonised by calcium gluconate via lowering the threshold potential of myocardial cells thereby normalising the difference between the membrane potential and the threshold potential.[15] Administration of glucose/insulin and/or salbutamol may lower the plasma potassium level by promoting cellular influx. Haemodialysis is indicated in patients with renal failure. Our patient did not respond to either calcium gluconate and plasma potassium lowering medication. An explanation for this might be the ongoing and massive cellular potassium efflux.

Whether toxicity might be prevented by slower infusion rates is unclear. As noted above, the relationship between the infusion rate of AmB and the development of (cardiac) toxicity is not unequivocal. However, some authorities argue that infusion rates of four to eight hours are safe and probably without noticeable toxicity.[16] Whether continuous infusion over 24 hours might further reduce toxicity is unclear. Indeed, continuous infusion of C-AmB over 24 hours has shown to reduce (nephro)toxicity;[17,18] however, efficacy may be decreased due to lower peak serum levels.[19] Discontinuation of (liposomal) AmB should be considered when suspected related hyperkalaemic episodes have occurred provided that the fungus is susceptible to alternative antifungal drugs.

CONCLUSION

The acute onset of severe hyperkalaemia with concomitant cardiac arrhythmias is a rare but life-threatening side effect related to infusion of both C-AmB and L-AmB. Clinicians should be aware of this adverse reaction when prescribing this drug. Although higher infusion rates do not increase toxicity per se, slower administration over more than two hours might be considered. Discontinuation of (liposomal) AmB should be considered when suspected related hyperkalaemic episodes have occurred.

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CASE REPORT

Renal failure due to acute phosphate nephropathy

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ABSTRACT

Case report of a 62-year-old woman who developed acute renal failure due to nephrocalcinosis, also called acute phosphate nephropathy, after large bowel cleansing in preparation for colonoscopy using oral sodium phosphate solution (Phosphoral, de Witt, Cheshire, UK). Subsequently her renal insufficiency resolved only partially resulting in stage 4 chronic kidney disease. In retrospect multiple risk factors for this condition (hypertension, diuretics, AT-II receptor blocker, female gender, advanced age and volume depleting due to vomiting and nausea) were identified. If these factors had been taken into consideration prior to prescribing this drug, acute and chronic renal failure would have been prevented. Future investigation of potential risk factors and the exact mechanism of this complication is necessary to identify those patients prone to develop this complication. In the meantime prescribing physicians should be made aware of this complication. On the basis of the current state of knowledge the evidence seems to be quite compelling not to prescribe these drugs in patients with one or more associated risk factors. It could even be argued that these drugs should not be prescribed at all.

KEYWORDS

Acute renal failure, nephrocalcinosis, oral sodium phosphate solution, phosphate nephropathy

INTRODUCTION

Acute renal failure due to nephrocalcinosis after large-bowel cleansing with sodium phosphate preparations prior to endoscopic procedures is a rare and easily overlooked diagnosis. The estimated risk of acute kidney failure after the use of oral sodium phosphate preparation is 1.14 to 2.35 (OR).[1,2] The main reasons for not diagnosing this condition are unfamiliarity with this complication, the time lag between the ingestion of the drug and the onset of renal failure and the fact that the acute as well as the chronic renal failure which results from this ingestion is not routinely checked for.

CASE REPORT

A 62-year-old woman was referred to our dialysis centre for acute renal failure of three days duration, which did not respond to conservative treatment and volume loading.
Her previous history was unremarkable with the exception of a hysterectomy and hypertension, which was managed with diuretics and an AT-II receptor blocker. She had undergone an ileocolonoscopy three days prior to presentation at our hospital for the analysis of abdominal pains of several months duration. Bowel cleansing for this procedure had been performed using 90 ml of oral sodium phosphate solution (OSPS, Phosphoral, de Witt, Cheshire, UK). This did not result in any complaints other than some nausea and several episodes of vomiting. Immediately after the endoscopy she developed atrial fibrillation with hypotension (85/45 mmHg), which resulted in admission for observation and treatment with volume loading and a bolus of digoxin. Within a few hours she converted back to sinus rhythm and her blood pressure normalised (150/80 mmHg). At admission, an increase of a pre-existent creatinine value taken three years earlier was noticed after colonoscopy: 73 to 175 µmol/l. In the following days, renal failure was progressive despite adequate volume loading and adequate blood pressure (day 3 creatinine 333 µmol/l). She was then referred to our centre for possible dialysis.
On physical examination a female patient in no obvious distress with a blood pressure of 145/75 was observed.

There were no signs of either hypovolaemia, or volume overload, nor were there signs of pericarditis. Physical examination was completely unremarkable.

Laboratory test results showed elevated levels of creatinine and urea (325 µmol/l and 10.9 mmol/l). All other laboratory values where within the normal range including phosphorus and calcium (1.29 and 2.27 mmol/l). Urinalyses showed no sign of proteinuria or erythrocyturia and a urine sodium concentration of 24 mmol/l. The kidneys were normal on ultrasound examination. A kidney biopsy was performed on day 10 after colonoscopy (creatinine 390 µmol/l), demonstrating more than 10 glomeruli with a normal aspect. The immunofluorescence was negative for immunoglobulins as well as for complement factors. However, on light microscopy, the tubulointerstitium was abnormal with diffuse nonpolarising tubular deposits. These deposits were surrounded by degenerative changes of the epithelium and locally loss of a few cells combined with focal mitotic activity. The interstitium showed no deposits, nor was there any inflammatory infiltration. Von Kossa staining on the tubular deposits was positive, which established the diagnosis of acute nephrocalcinosis, also known as acute phosphate nephropathy (*figure 1*).

Supportive treatment was given and eventually the creatinine level decreased gradually over several weeks after reaching a creatinine peak of 438 µmol/l at day 11 after colonoscopy. On her visit to the outpatient clinic three months after admission, the renal failure had stabilised at a creatinine level of 160 µmol/l (chronic kidney disease stage 4, estimated creatinine clearance 25 ml/min by Cockcroft-Gault formula (female 62 years, 50 kg) and 28 ml/min by MDRD formula) (*figure 2*).

Figure 1. *Von Kossa staining showing tubular calcium deposit*

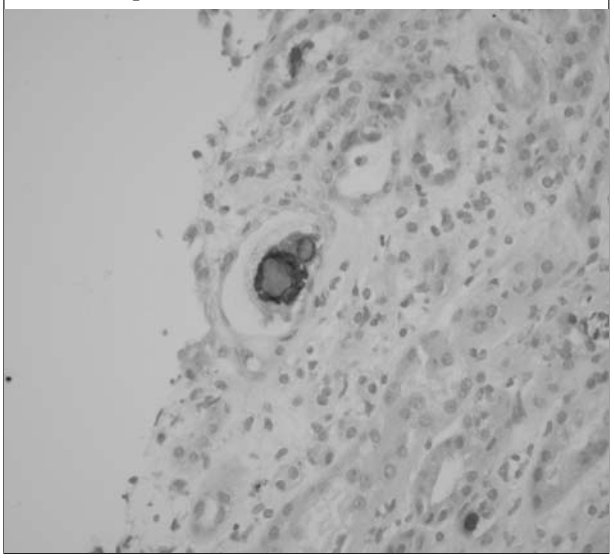
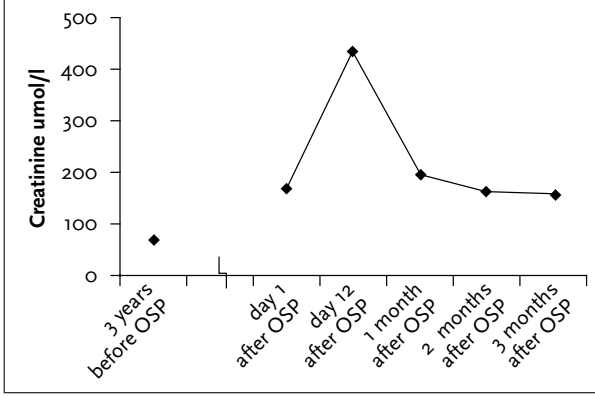


Figure 2. *Course of acute renal failure after oral sodium phosphate (OSP) preparation for colonoscopy*



DISCUSSION

In this case report a patient is presented who developed acute renal failure due to biopsy-proven nephrocalcinosis after the use of oral sodium phosphate during preparation for an elective colonoscopy. Chronic tubulointerstitial nephropathy due to nephrocalcinosis is a well-known histopathological entity associated with chronic hypercalcaemia. Acute nephrocalcinosis has also been described previously as a complication after the use of oral sodium phosphate solution (OSPS) or phosphorus-containing medications.[3-10] Acute phosphate nephropathy has been chosen as the term to describe this condition. A retrospective cohort study has identified 21 cases of acute phosphate nephropathy among 7349 kidney biopsies.[3] In this study the condition has proven to be partially reversible, but residual renal insufficiency persisted in all described cases. However, this might partially have been due to case selection.

The phosphorus concentration is regulated by the oral phosphorus load and renal excretion. Absorption in the gut takes place for up to 60% in the upper duodenum, jejunum and ileum by active (calcitriol dependent) and passive transport. Compared with a normal daily dietary phosphorus intake of 1.5 g, a 45 ml bottle of OSPS (as used in the Netherlands) contains 24.4 g of monobasic sodium phosphate and 10.8 g of dibasic sodium phosphate (two gifts of 45 ml are given in bowel preparation). These amounts of phosphorus lead to an almost 100% rise in serum phosphate concentration on the day after ingestion.[11] Hyperphosphataemia due to sodium phosphate enemas has been described in children but in adults this is a rare complication, although hypertonic sodium phosphate enemas can be absorbed and be life-threatening.[12] Martin[13] showed that normal doses of enema solution (containing 21 g sodium biphosphate and 7.9 g of sodium phosphate)

cause measurable changes in serum phosphorus level. In a pig model enema solutions at a dose of 20 to 30 ml/kg were uniformly fatal.[13]

However, there are no solid published data on the exact amount of intestinal phosphate absorption after OSPS. Only a letter describing five healthy volunteers showed an average intestinal uptake of 43% of the ingested dose of phosphorus.[14] The kidneys play an important role in the regulation of plasma phosphorus leading to high urinary phosphate excretion.[11] When the urine gets supersaturated and inhibiting factors such as pH, citrate and pyrophosphate concentrations are low, crystallisation will take place. The calcium phosphate crystals bind to the tubular epithelial cells causing reactive oxygen damage.[15] This is the supposed main pathway which leads to the renal impairment.

In phosphate nephropathy nonpolarising tubular calcium phosphate deposits are typically found on histological examination. The von Kossa staining, accentuating the phosphate component, is positive. This is combined with normal glomeruli, mildly to none affected interstitium and tubular epithelial cells showing signs of degenerative changes.[3,5,7,9] All of these histological findings were present in our case.

Patients who are volume depleted are more prone to develop acute phosphate nephropathy when using OSPS. For this reason ulcerative colitis and diarrhoea are relative contraindications for the use of OSPS. Medications contributing to renal hypoperfusion such as diuretics, ACE inhibitors and AT-II receptor blockers could also predispose to this disorder. Other risk factors which have been suggested are advanced age, diabetes, renal impairment and female gender.[1,2,16] A retrospective analysis of a single-centre database (n=286) showed an absolute decline in glomerular filtration rate of up to 6 ml/min over a period of six months in the OSPS group compared with 1% in the control group, who did not undergo colonoscopy, over a period of one year.[17] These groups where equally matched for gender, age, race, comorbidity and the use of several medications (ACE inhibitors, AT-II receptor blockers and diuretics). Furthermore these groups had creatinine levels which where in the normal range (<130 µmol/l) at baseline. Linear regression analysis marked ACE inhibitors, AT-II receptor blockers and diabetes as significant determinants of glomerular filtration loss. *Table 1* shows the combined risk factors as described in six studies with a total of 488 cases of renal failure secondary to OSPS.

On the basis of these data, our 62-year-old female patient with mild hypertension managed with diuretics and an AT-II receptor blocker and possible volume depletion due to vomiting had a high risk for developing this complication.

We consider prospective studies to formally assess the risk for developing this partially irreversible complication and to formally define relevant risk factors unethical since multiple safe alternative agents are available. It is therefore considered relevant to report individual cases to national and/or international pharmacovigilance databases. In the meantime, physicians prescribing these drugs should be aware of the associated risks. As mentioned by others, oral sodium phosphate purgatives should not be used in patients with chronic kidney disease stage 3-5.[17,18] With the growing numbers of studies reporting about this complication in patients with stage 1-3 chronic kidney disease and even with normal renal function, there seems to be compelling evidence not to use this kind of purgative in patients with known risk factors.

Table 1. *Risk factors for acute phosphate nephropathy as found in 6 studies with 488 cases of renal impairment*

Study	N° of cases	RI due to OSP	Risk factors	Odds ratio
J Am Soc Nephrol, Hurst et al, 2007	9799	83	Age, HT, DM, ACVD, CHF, ACE, ARB, diuretics	2.35
J Am Soc Nephrol, Markowitz et al, 2005	7349	21	Volume depletion, female gender, ACE ARB, diuretics, HT, age, CKD	NA
Am J Gastroenterol, Russmann et al, 2007	2083	79	CKD, age, African American race, HT, ACE, ARB, diuretics	1.14
Arch Intern Med, Khurana et al, 2008	286	286	DM, ACE, ARB, age	NA
Arch Pathol Lab Med, Gonlusen et al, 2006	19	19	HT, ACE, ARB, diuretics	NA
Am J Gastroenterol, Sica et al, 2007	NA	NA	Age, female gender, CKD, ACE, ARB, volume depletion, diuretics	NA

RI = renal impairment; OSP = oral sodium phosphate; HT = hypertension; DM = diabetes mellitus; ACVD = atherosclerotic cardiovascular disease; CHF = chronic heart failure; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; NA = not available.

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Netherlands
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PHOTO QUIZ

An ECG with U waves

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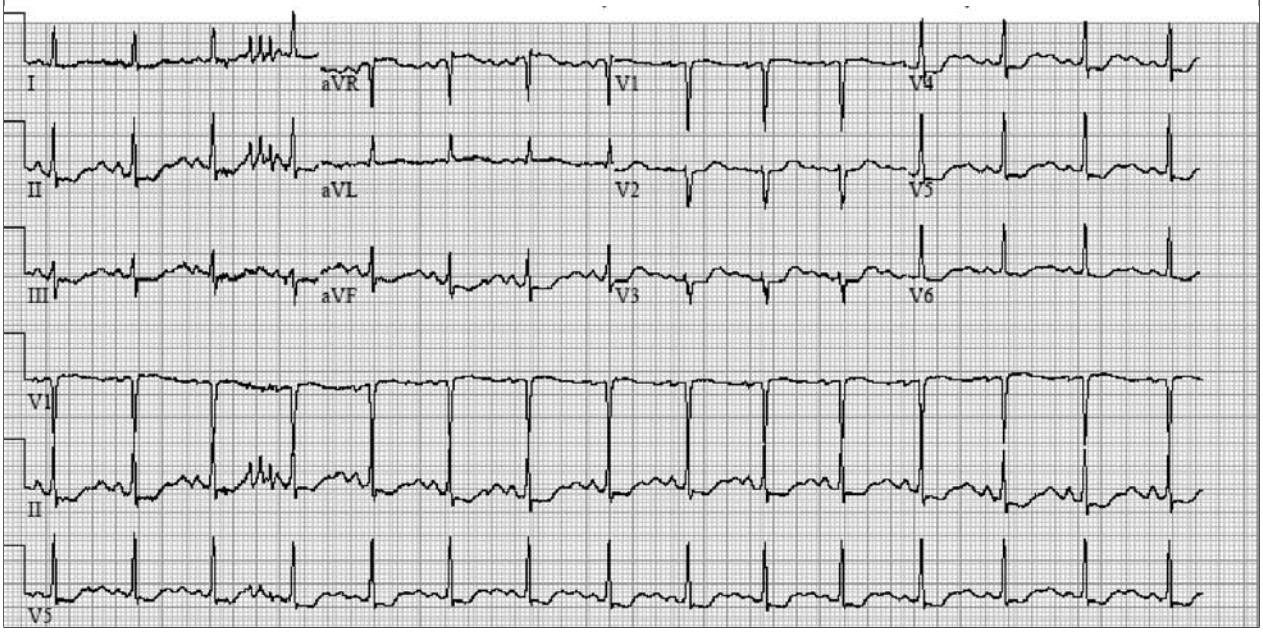
CASE REPORT

A 45-year-old woman was seen on the emergency ward because of muscular weakness for several weeks. Her medical history revealed hypertension and constipation, for which she was taking hydrochlorothiazide and furosemide (both prescribed by her physician), and laxatives. At admission the patient was responding normally and the physical examination revealed no abnormalities. An ECG was taken (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 443 for the answer to this photo quiz.

Figure 1. *ECG at admission, showing low T waves in leads I, aVL, and V_1, U waves in leads V_2 to V_6 and ST depression in leads II, II, aVF, and V_3 to V_6 (some artefacts are seen in I and II)*



ANSWER TO PHOTO QUIZ (ON PAGE 442)

AN ECG WITH U WAVES

DIAGNOSIS

The laboratory results revealed a hypokalaemia of 1.7 mmol/l (normal range 3.5 to 5.0 mmol/l), a metabolic alkalosis (pH 7.52, HCO_3 30 mmol/l) and a slight hypochloraemia. The ECG abnormalities (especially the U waves) are seen in patients with severe hypokalaemia. U waves can also be seen in hypercalcaemia, with antiarrhythmic drugs, in thyrotoxicosis, intracranial hemorrhage, exercise and in the congenital long-QT syndrome. The low T waves and ST depression are also seen in severe hypokalaemia, but myocardial ischaemia should be considered. The patient did not complain about chest pain and the cardiac enzymes were normal, so myocardial ischaemia does not seem to be present. The hypokalaemia (and the metabolic alkalosis) were probably caused by the use of excessive amounts of diuretics and laxative abuse.[1] Primary hyperaldosteronism was excluded. The patient is seen by a psychiatrist.

After treatment of the hypokalaemia, the ECG normalised (*figure 2*).

The severity of the manifestations of hypokalaemia tends to be proportionate to the degree and duration of the hypokalaemia. Symptoms generally do not become manifest until the serum potassium is below 3.0 mmol/l and usually resolve with correction of the hypokalaemia. Clinical manifestations are severe muscle weakness or paralysis, rhabdomyolysis, renal abnormalities, cardiac arrhythmias and ECG abnormalities. Cardiac arrhythmias and ECG abnormalities are, for instance, premature, atrial and ventricular beats, atrioventricular block, intraventricular conduction abnormalities and ventricular arrhythmias. Hypokalaemia can be life-threatening, especially in patients with coronary artery disease. Treatment should be correction of the potassium and treatment of the underlying cause.[2]

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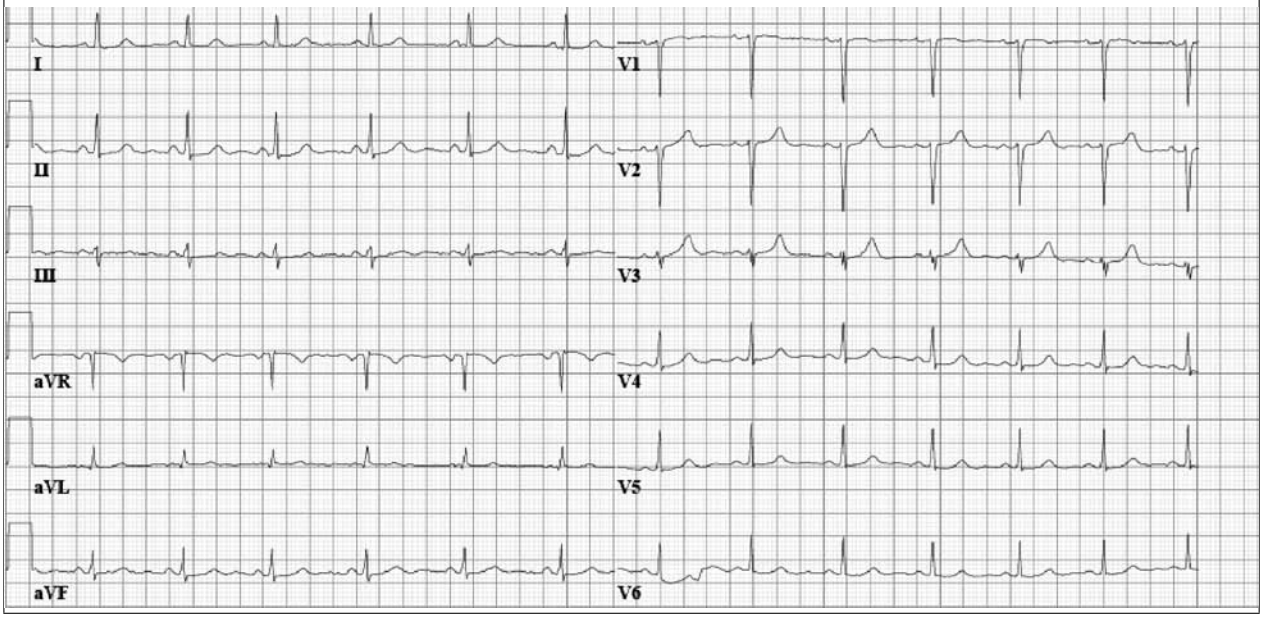
Figure 2. *Normalised ECG after treatment of the hypokalaemia*



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A 75-year-old woman presenting to the emergency department with backache and respiratory distress

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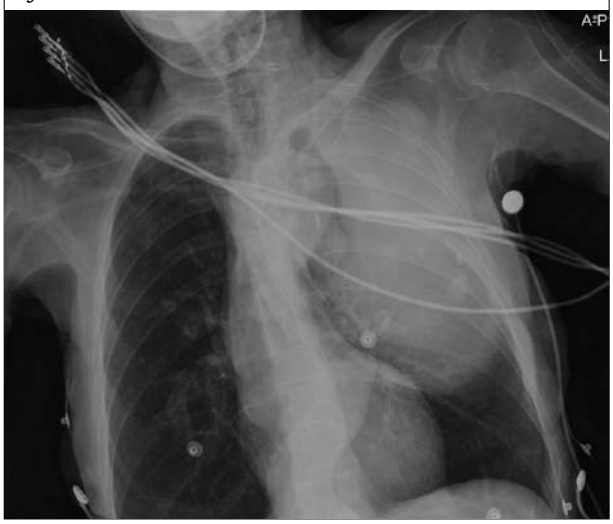
CASE REPORT

A 75-year-old female patient presented to the emergency department with complaints of backache and respiratory distress. Her medical history revealed hypertension and a myocardial infarction three weeks earlier, for which she was taking carbasalate calcium and clopidrogel. At presentation she was responsive, adequately and haemodynamically stable. Her arterial oxygen level was 98% with 5 liters of oxygen supplied by a nasal catheter. Chest X-ray showed a broadened mediastinum, a large non-specific density in the left upper part of the thoracic cavity and a tortuous outline of the thoracic aorta (*figure 1*).

Figure 1. *Chest X-ray on admission showing a broadened mediastinum, a large density in the upper left part of the thoracic cavity and a tortuous outline of the thoracic aorta*



WHAT IS YOUR DIAGNOSIS?

See page 445 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (ON PAGE 444)

A 75-YEAR-OLD WOMAN PRESENTING TO THE EMERGENCY DEPARTMENT WITH BACKACHE AND RESPIRATORY DISTRESS

DIAGNOSIS

The chest X-ray showed a large subpleural haematoma in the left upper part of the thoracic cavity, which was suspected to be caused by a ruptured thoracic aneurysm. Moreover, laboratory tests revealed a severely decreased haemoglobin level of 4.6 mmol/l (normal range 7.5 to 9.8 mmol/l).

To confirm this diagnosis, computerised tomography (CT) was performed immediately after the chest X-ray. It showed a saccular aneurysm of the thoracic aorta, with an extraluminal diameter of 1.9 cm, located in the distal part of the aortic arch. Apparently, the aneurysm had ruptured into the left extrapleural space, between the parietal pleura and thoracic wall, producing a large haematoma of 13 x 8 x 20 cm and subsequent compression atelectasis of the left lung, which contributed to the respiratory distress (*figures 2* and *3*). A 4.2 cm asymptomatic infrarenal abdominal aneurysm was detected as well. This life-threatening ruptured aneurysm was treated immediately with a GoreTAG® endovascular graft, covering both the aneurysm and the left subclavian artery (*figure 4*). The extrapleural haematoma was evacuated by thoracocentesis. Due to collateral circulation, there was no circulatory impairment of the left arm. The patient needed multiple blood transfusions. After two days of observation on the intensive care unit she could be discharged to the medical ward. Unfortunately, the procedure was complicated by a stroke, with left-sided hemiparesis and paraparesis of the legs. After 40 days she was discharged to a nursing home, communicating well but in a severely disabled physical condition.

Extrapleural haematoma is a rare condition characterised by a collection of blood between the pleura parietalis and the thoracic wall, mostly due to life-threatening conditions such as a (traumatic) aortic aneurysm rupture. In this patient the bleeding had been delayed due to the effort needed to leak into this non-existing space. Obviously, bleeding into a non-existing space requires more effort and time than leakage into, for example, the pleural cavity. If the aneurysm had ruptured into the pleural cavity itself, the patient would most likely have died immediately from a hypovolaemic, haemorrhagic shock. Containment of rupture of a thoracic aneurysm is the only chance of survival.

Figure 2. *Thoracic CT scan (axial slice) showing the saccular aneurysm (arrow) and haematoma in the extrapleural space*

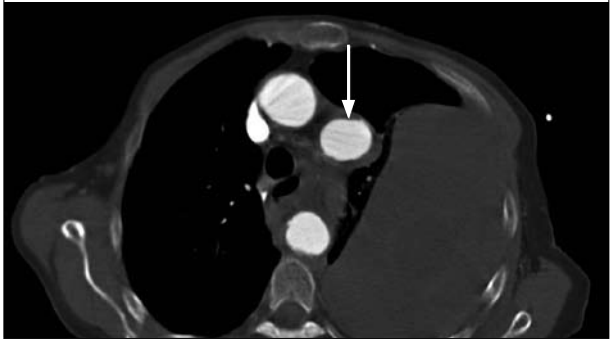


Figure 3. *Intraoperative angiography image of the aortic arch*

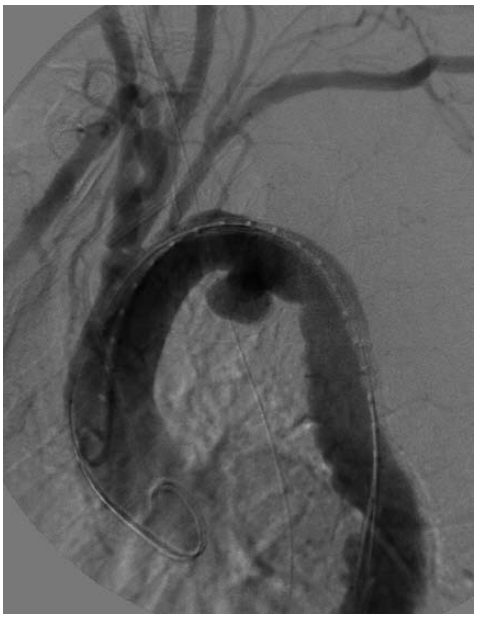
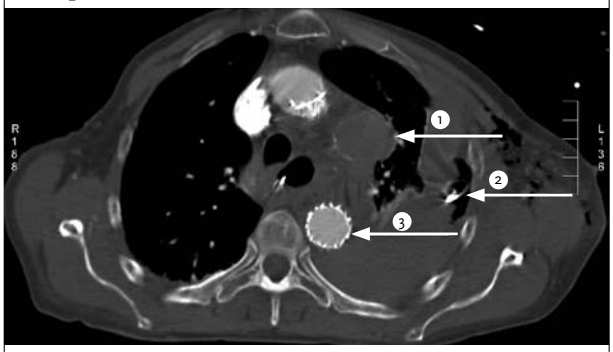


Figure 4. *Thoracic CT scan one day after admission showing the repaired aneurysm with the GoreTAG® endoprothesis in situ*



The aneurysm is completely excluded as contrast is no longer leaking into in aneurysm (arrow 1). The extrapleural haematoma was evacuated by thoracocentesis (arrow 2). Arrow 3 shows part of the stent graft combination in the descending aorta.

MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the July-August issue of the Netherlands Journal of Medicine 2008 (available online on PubMed since 28 July 2008).

Article	Hits
EDITORIAL	
Double balloon scope for endoscopic retrograde cholangiopancreatography	110
REVIEW	
Encapsulating peritoneal sclerosis in patients on peritoneal dialysis	151
ORIGINAL ARTICLE	
Double balloon enteroscopy for endoscopic retrograde cholangiopancreaticography after Roux-en-Y reconstruction: case series and review of the literature	165
CASE REPORTS	
Liver transplantation in a patient with encapsulating peritoneal sclerosis	123
Myomatous erythrocytosis syndrome: further proof for the pathogenic role of erythropoietin	199
Two rare complications of glioblastoma multiforme: persistent hiccup and acquired haemophilia A	104
SPECIAL REPORTS	
Case reports: added value counts	92
The *Netherlands Journal of Medicine*: 1998-2002, what came out of it?	91
Treatment of chronic hepatitis B virus infection – Dutch national guidelines	227
Treatment of chronic hepatitis C virus infection – Dutch national guidelines	143
PHOTO QUIZZES	
Sudden onset of dorsal swelling of hands and feet	296
Binocular vertical double vision in a diabetic patient	131
MONTHLY NJM ONLINE HITLIST	
For all articles published in April 2008	73
AWARD FOR THE BEST ARTICLE	
Published in the *Netherlands Journal of Medicine* in 2007	84

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SPECIAL REPORT

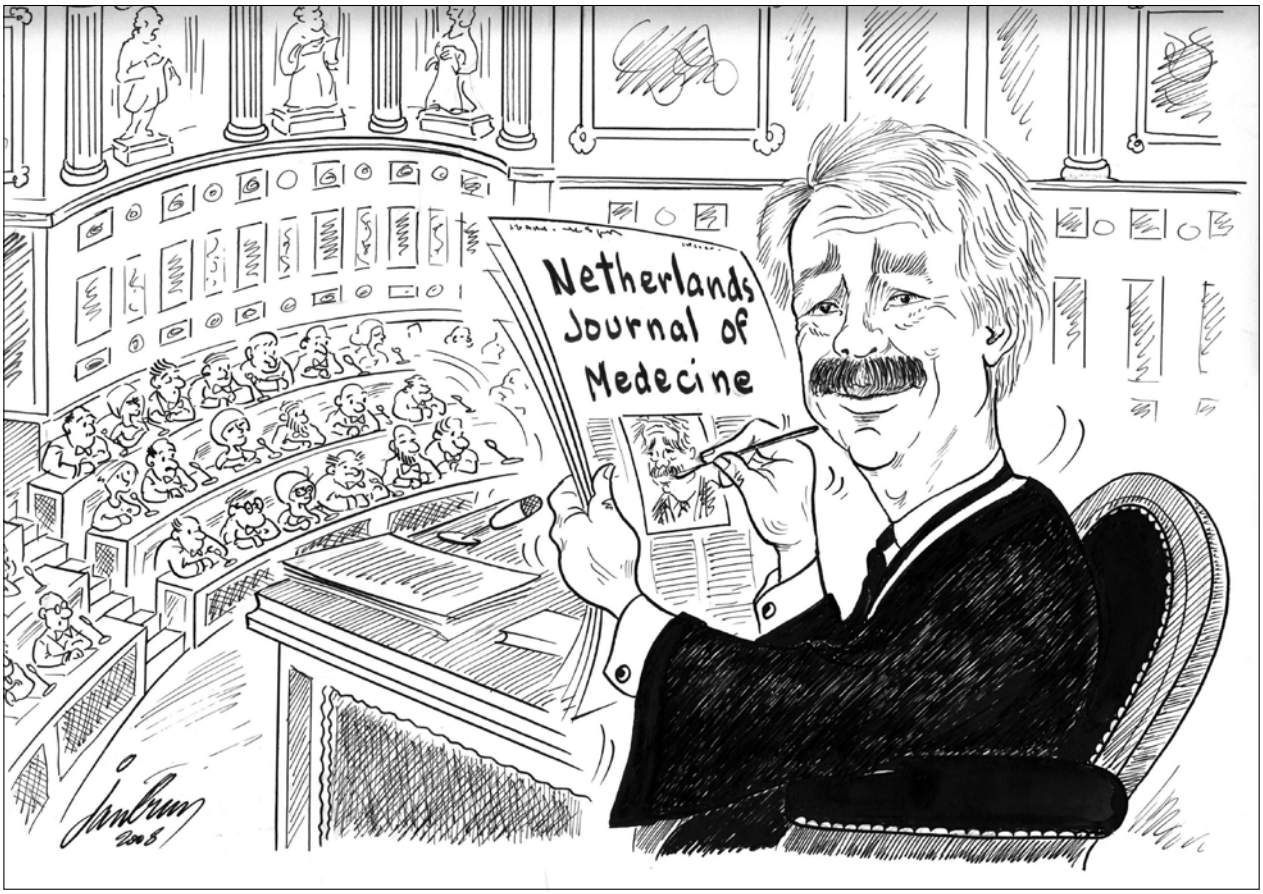
Reshaping the journal: editorial board 2002-2005

Anton Stalenhoef

Theo Thien

Paul Smits

Geeralien Derksen-Willemsen



Aims and scope
The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

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Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process, number the lines in the margin and the pages.
Subheadings should not exceed 55 characters, including spaces.
Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for generic names of substances and materials.
A *Covering letter* should accompany the manuscript, identifying the corresponding person (with the address, telephone number, fax number and e-mail address). Conflicts of interest, commercial affiliations, consultations, stock or equity interests should be specified. In the letter one to three sentences should be dedicated to what this study adds. The letter should make it clear that the final manuscript has been seen and approved by all authors. All authors should sign the letter. The letter should either be submitted through http://mc.manuscriptcentral.com/nethjmed or faxed to the editorial office (+31 (0)24-354 17 34).

Divide the manuscript into the following sections: Title page, Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

The *Title page* should include authors' names, degrees, academic addresses, correspondence address, including telephone number, fax number, e-mail address and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs: Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

Keywords: Include three to five keywords.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely, without discussion.

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

Acknowledgement: All funding sources should be credited here. Also a statement of conflicts of interest should be mentioned.

References should be numbered consecutively as they appear in the text (after the punctuation and in square brackets). Type the reference list with double spacing on a separate page. References should be in the language they are published in, conform the 'Vancouver' style for biomedical journals (N Engl J Med. 1991;324:424-8).

Journal abbreviations should conform to the style used in the Cumulated Index Medicus. Examples:

1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med. 2001;59:184-95.
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LETTER TO THE EDITOR

Severe skin necrosis after rituximab-CHOP therapy

The cancer chemotherapeutic drug doxorubicin is known for its severe acute local complications after extravasation.[1] Rituximab is a monoclonal antibody directed against the CD20 antigen on B lymphocytes, used to treat CD20 positive non-Hodgkin lymphomas, often in combination with CHOP therapy (cyclophosphamide, doxorubicin, vincristine, prednisolone). Although it is a frequently administered drug, no severe toxic effects have been described yet after extravasation of rituximab.[2] We describe a patient with severe toxicity in the arm after extravasation of rituximab, followed by CHOP therapy in the contralateral arm.

A 76-year-old woman with a diffuse B-cell non-Hodgkin's lymphoma started her first treatment with R-CHOP (rituximab combined with CHOP). During infusion of rituximab, extravasation of rituximab was observed at the infusion site and local erythema and oedema developed. The following day, CHOP therapy was administered via the opposite arm. However, the lesion was progressive and ulceration and necrosis developed over time, complicated by subcutaneous and muscular necrosis. Therefore, surgery was needed with resection of necrosis and skin grafting (*figure 1*).

To our knowledge, no severe local toxic effects have been described after extravasation of rituximab. However, a case of Stevens-Johnson syndrome (erythema exsudativum multiforme major) has been reported after treatment with rituximab in a patient with relapsed follicular lymphoma.[3] Nevertheless, this case describes a diffuse dermatological condition, not related to extravasation.

Doxorubicin is a highly vesicant anthracycline anticancer drug. Extravasation can lead to severe necrosis of the skin and soft tissues.[1] Vincristine is a non-DNA binding vesicant drug, which belongs to the group of vinca alkaloids. These agents are cleared more easily from extravasation sites and cause less tissue damage than DNA-binding agents (such as doxorubicin).[1] Cyclophosphamide belongs to the group of alkylating agents and is an irritant drug, which means it is not a vesicant drug.[1]

Figure 1. *Skin lesion right arm, 64 days after extravasation and after treatment by resection of necrosis, skin grafting and vacuum assisted closure therapy*

Only extravasation of rituximab occurred in this patient, and a new side effect of rituximab can therefore not be excluded. However, the clinical presentation and development of the arm lesion closely resemble the toxicity of doxorubicin. This may point towards a recall phenomenon.[4] Extravasation of rituximab caused local inflammation. The following administration of doxorubicin in the contralateral arm might have resulted in increased levels of doxorubicin locally at the site of inflammation, leading to subcutaneous and muscular necrosis. Toxic recall effects of doxorubicin have been described earlier after previous use of doxorubicin, after radiotherapy and diffuse sunburn.[4-6]

In conclusion, caution is advised when the administration of doxorubicin is considered in patients with local inflammation due to previous extravasation.

ACKNOWLEDGEMENT

We would like to acknowledge J. Dokter, medical coordinator of the Burns Centre and L. Ruijgrok, pharmacist, both from the Medical Centre Rijnmond-Zuid, for their contributions.

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