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Efficacy and safety of inhaled insulin

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Oxybutynin for hyperhidrosis

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EDITORIAL

Assessment of a new rapid urease test (GUT test) to diagnose *Helicobacter pylori* infection

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Making a diagnosis is an important process in medicine. Performing a diagnostic test will ascertain the presence of a disease as a cause of a health problem. The value of test results depends both on the diagnostic performance and how the results will improve the outcome of illness. Diagnostic performance means that the test should evaluate what it intends to assess, and that repeated measurements give similar results. Besides performance, the diagnostic test will be chosen because of several other factors such as preferences, availability, experience, costs and so on.

Inappropriate diagnostic testing may have serious consequences for individual patients. To prevent the implementation of disappointing new diagnostic tests it is necessary to conduct appropriate assessment studies. In the current issue of the Netherlands Journal of Medicine, colleague van Keeken from Bernhoven Hospital, Oss, the Netherlands presents a study in which she and her colleagues evaluated a new rapid urease test (GUT test) to diagnose *Helicobacter pylori* infection.[1] Guidelines have been put forward for evaluating new diagnostic tests.[2] According to these guidelines three aspects are of major importance: selection of an appropriate patient population, determination of the diagnostic performance and the relation with existing diagnostic tests. Let us apply these aspects to van Keeken's study.

CLINICAL INDICATION

The initial challenge lies in the selection of an adequate patient population. The risk of not using the appropriate patient population is that the large contrast between severely ill patients and healthy individuals will overestimate the test performance. What is the appropriate patient population for a *H. pylori* test? The infection is without doubt involved in several diseases: peptic ulcer disease, gastric cancer and B cell lymphoma.[3] The impact of *H. pylori* infection and functional dyspepsia is more controversial. *H. pylori* eradication does appear to be beneficial for a small subgroup of patients with functional dyspepsia.[4] Thus, the indication to use the test is patients suspected of having peptic ulcer disease, gastric cancer, B cell lymphoma and in all probability functional dyspepsia. This, however, means that patients referred for upper gastrointestinal endoscopy are not the indicated study population. The patient population evaluated in this study consisted of 116 consecutive patients who underwent an upper gastrointestinal endoscopy. More data about the indication for *H. pylori* infection testing or upper gastrointestinal endoscopy were not given. Because of this lack of information about the reason for testing it is not possible to judge whether the test has been evaluated in an adequate patient population.

DIAGNOSTIC PERFORMANCE

There are several ways to handle the diagnostic test results from an assessment study. For qualitative tests sensitivity, specificity, and positive and negative predictive value are the most used test outcome measures. The major problem with assessment of the diagnostic performance of the *H. pylori* test is the absence of a test determining the definitive disease status (gold standard). As a result in some studies inappropriate tests are being used as a reference. In this study the authors have overcome the problem by comparing the new test directly with another rapid urease test (CLO test), and with the combination of bacterial culture and histology. Previous research has shown that using a combination of biopsy-based tests represents an appropriate reference standard to diagnose *H. pylori* infection.[5]

CONTRIBUTION OF THE NEW TEST

When it becomes clear that the diagnostic performance is adequate in the indicated patient population it is important to establish the contribution of the new test to the existing diagnostic arsenal. At the moment several methods can be used to diagnose *H. pylori* infection, both biopsy based and nonbiopsy based. The rapid urease test evaluated in this study requires an upper gastrointestinal endoscopy for retrieval of a biopsy specimen. The other biopsy-based tests are bacterial culture and histology. The results from the study showed that the overall diagnostic performances of the evaluated biopsy-based tests were not statistically different. So other aspects of the new test are of importance. The authors state that the new rapid urease test has a more rapid reaction time and is much cheaper. The outcome of the new rapid urease test (GUT test) was reliable 60 minutes after endoscopy in comparison with 24 hours for the other urease test (CLO test) and several days for culture and histology. It is, however, questionable whether this gain of time has significant clinical consequences. Another important aspect is the lower costs of the test in comparison with other rapid urease tests. *H. pylori* infection is still a major health problem worldwide.[6] A cheaper diagnostic test with equal clinical effects might lead to significantly lower overall medical costs.

CONCLUSION

The new more rapid urease test seems to be a promising new diagnostic test with equal diagnostic performance but considerably lower costs and a faster availability of the test results, in comparison with other biopsy-based *H. pylori* tests. Whether the gain in time and lower costs are sufficient to switch from the old but well-known other rapid urease tests to this new more rapid GUT test depends on the priorities and preferences of the users. However, before implementation the results from this study have to be confirmed, including the additional value of the new test to the entire diagnostic process and the cost-effectiveness.

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REVIEW

Efficacy and safety of inhaled insulin in the treatment of diabetes mellitus

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ABSTRACT

Many patients with diabetes mellitus view subcutaneous injections of insulin as a daily burden. Pulmonary delivery of insulin offers an alternative route of administration and may as such improve diabetes treatment. Inhaled insulin provides a rapid absorption of insulin, but with low bioavailability. Phase III clinical trials in type 1 and type 2 diabetes have disclosed clinical equivalence between three inhaled insulin products (Exubera, AERx iDMS, and HIIP) and regular human insulin, both in terms of glycaemic control and hypoglycaemic risk. Inhaled insulin cannot be used to replace basal insulin requirements. The most commonly reported adverse effects of inhaled insulin are cough and insulin antibody formation, the clinical significance of which is uncertain. No or minimal deterioration in pulmonary function parameters have been recorded, although studies were typically of short duration. Patients participating in inhaled insulin trials generally expressed satisfaction with the product and chose to remain on it. The availability of inhaled insulin may increase willingness in type 2 diabetic patients to consider insulin therapy. More studies of longer duration are required to determine (pulmonary) safety and cost-effectiveness of inhaled insulin, and to disclose which patients may benefit the most.

KEYWORDS

Diabetes mellitus, glycaemic control, hypoglycaemia, inhaled insulin, treatment

INTRODUCTION

More than 80 years ago, Banting and Best introduced therapeutic insulin into clinical practice. They were able to extract the hormone and inject it into a 14-year-old boy diagnosed with type 1 diabetes, saving him from premature death.[1] Currently, a wide range of injectable insulin products are available for the treatment of diabetes, which are being used by millions of patients with type 1 and type 2 diabetes worldwide. These products include short- and immediate-acting preparations to be used during mealtimes, intermediate- and prolonged-acting agents intended to replace basal insulin requirements, and premixed formulations. Despite these various profiles, it has proved virtually impossible to replicate the physiological pattern of endogenous insulin secretion to maintain near-normal levels of glycaemia. Consequently, microvascular and macrovascular complications remain highly prevalent in both type 1 and type 2 diabetes.[2-4] In addition, despite advances in the development of smaller needles and patient friendly pen-injector devices to allow better tolerability of subcutaneous administration, injection of insulin is still viewed as a complicated and painful procedure.[5] The burden of three to six insulin injections daily may lead to avoidance to self inject, even in the absence of overt needle phobia.[6]

Attempts to develop noninvasive routes for insulin administration emerged soon after the introduction of insulin. Degradation by the acidic environment of the stomach or by digestive enzymes in the upper gastrointestinal tract, active mucociliary clearance and presence of proteolytic enzymes in the nasal cavity, and the relative impermeability of the skin have precluded successful delivery by oral, intestinal, intranasal, and transdermal routes.[7] None of these obstacles apply to pulmonary delivery of insulin. On the contrary, the lungs appear perfectly equipped for the absorption of small peptides such as insulin. The surface area of the alveoli

measures ~140 m² (corresponding to half a tennis court), and is lined by a very thin (0.1-0.2 μm), richly perfused, highly permeable monolayer of epithelium. In addition, the lungs are highly immunotolerant and largely lack mucociliary transport.[8] Interest in delivering insulin through the pulmonary tree originated in the 1920s.[9] In 1971, it was shown that inhalation of insulin resulted in a prompt increase in plasma immunoreactive insulin and a reduction in blood glucose levels in healthy and diabetic subjects.[10] Better understanding of aerosol dynamics and particle properties has contributed greatly to the current development of inhaled insulin preparations. Several pharmaceutical companies have collaborated with pulmonary drug delivery companies to develop an inhaled insulin product and corresponding inhalation system (*table 1*). At least one inhaled insulin preparation will soon be released on the (Dutch) market. The objectives of this review are to provide an overview of pulmonary insulin preparations in development, to discuss pharmacokinetics and safety of inhaled insulin, and – specifically – to critically evaluate results of clinical trials performed with inhaled insulin.

PHARMACOKINETICS

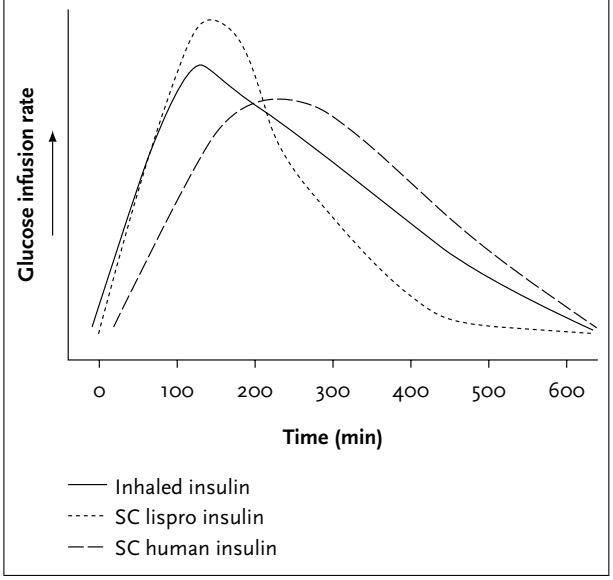
Several factors affect the pulmonary delivery of inhaled insulin. These include the efficiency of the inhaler, the size of the particles in the aerosol, and the breathing pattern. The efficiency of the inhaler device reflects the percentage of drug emitted from the device by correct inhalation, which is usually 80 to 95% for dry-powder inhalers, but can be as low as 20 to 30% for liquid nebulisers.[11] The optimal particle size for deep alveolar deposition is an aerodynamic diameter (a function of the geometric diameter and mass density) of 1 to 3 μm; larger particles, especially >10 μm, are primarily deposited in the upper airways or oropharynx, whereas smaller particles are mostly exhaled. The aerosol is best inhaled by slow inspiration with a large tidal volume. A good pulmonary function is a prerequisite for inhalation therapy. Performing a breath-hold of two to six seconds at the end of inspiration can improve collection efficiency of the alveolar region. Forced inspiration, however, has an adverse effect on alveolar deposition and leads to particle loss in the orolaryngeal region.[12] Transport of insulin across the alveolar wall probably occurs by a paracellular process, although the exact process is still incompletely understood.[11] There is evidence that only 20 to 40% of insulin deposited in the lung reaches the circulation. The remainder undergoes cytosolic biodegradation or exits the lung via the mucociliary escalator.[11] Smoking, both acutely and chronically, enhances the absorption of insulin. Smokers were found to have more than threefold higher peak insulin levels upon inhalation of a standard insulin dose, resulting in hypoglycaemia.[13] Under optimal conditions, bioavailability of inhaled insulin in nonsmokers is approximately 8 to 12%. Absorption of inhaled insulin occurs rapidly. The time to reach maximum insulin concentration and glucose-lowering effect is similar to that of subcutaneous short-acting insulin analogues and shorter than that of subcutaneous regular insulin (*figure 1*). The duration of action of inhaled insulin is four to six hours, slightly longer than short-acting analogues and slightly shorter than subcutaneously injected regular insulin.[14] These pharmacokinetic characteristics make inhaled insulin suitable as mealtime insulin.

Table 1. *Inhaled insulin products currently under development*

Developer	Partners	Type of product and inhaler	Trade name
Nektar therapeutics	Pfizer	Dry powder Passive inhaler	Exubera®
Aradigm	Novo Nordisk	Liquid aerosol Microprocessor-controlled inhaler	AERx® iDMS
Alkermes	Eli Lilly	Dry powder Passive inhaler	HIIP®
Aerogen	-	Liquid aerosol Passive inhaler	Aerodose®
Pharmaceutical Discovery Corporation	Mannkind	Dry powder microparticles Passive inhaler	Technosphere®
Dura Pharmaceuticals	-	Dry powder Electromechanical inhaler	Spiros®
Microdose Technologies	Elan Corporation	Dry powder	Microdose DPI®
Kos Pharmaceuticals	-	Dry crystals Propellant inhaler	Unknown
BioSante Pharmaceuticals	-	Coated dry particles	Bio-Air®
CoreMed	-	Liquid aerosol	Alveair®

HIIP = human inhaled insulin powder.

Figure 1. *Glucose infusion rate in healthy individuals after inhalation of insulin, subcutaneous injection of regular insulin, and subcutaneous injection of insulin lispro*[14]



PRODUCTS

Table 1 provides an overview of the pulmonary insulin delivery systems that are currently being studied. Most systems are being developed by a joint venture between the manufacturer of inhalation devices and a pharmaceutical company that produces the insulin preparations. The insulin preparation is either a dry-powder or a liquid formulation. Dry-powder formulations have superior room-temperature stability, can deliver more insulin per inhalation, and are less prone to microbial growth, whereas liquid aerosol formulations are less susceptible to the influence of external humidity on dispersion. The products are in various stages of development, three of which have been tested in phase III clinical trials. The results of these trials will be discussed in more detail.

Exubera

The most thoroughly investigated inhaled pulmonary insulin system is Exubera, which consists of a dry-powder formulation with regular insulin (approximately 60%) and stabilisers, primarily mannitol, packaged in 1 and 3 mg blisters that contain 28 and 84 units of insulin, respectively. After placing a blister in the slot of the inhaler, the insulin is dispersed into an aerosol in a spacer reservoir, from which it can be subsequently inhaled. The bioavailability of the Exubera system is 9% and the biological efficiency (i.e. the blood glucose lowering effect) is 10 to 11% compared with subcutaneously injected insulin.[14] Thus, 1 mg of Exubera is comparable with approximately 3 units of subcutaneous insulin.

Studies that reported on the clinical efficacy of Exubera in type 1 diabetes include one small 12-week proof of concept study[15] and two larger randomised trials (follow-up six months),[16,17] involving 735 patients in total. In these studies, the experimental group received inhaled insulin at mealtimes in combination with either subcutaneous ultralente insulin once daily or NPH insulin twice daily. The comparator group either continued their subcutaneous insulin regimen of two to three insulin injections[15,16] or received mealtime regular insulin in combination with NPH insulin twice daily.[17] Insulin analogues were not used in either of these studies. Basal insulin replacement therapy was only identical in the experimental and comparator group in one study.[17] The mean daily dose of inhaled insulin ranged from 9.6 to 12.4 mg at initiation and increased slightly during the study to 10.8 to 14.2 mg.[16,17] From these data it can be calculated that, on average, the majority of patients used at least two to three blisters to meet insulin requirements at mealtimes. Inhalation therapy was found to be clinically equivalent to subcutaneous insulin treatment in all three studies. Over six months of treatment, HbA_{1c} values fell by 0.2 to 0.3% in patients randomised to inhaled insulin and by 0.16 to 0.4% in patients randomised to subcutaneous insulin, differences that obviously were not statistically significant.[16,17] Fasting plasma glucose values decreased slightly more in the inhaled insulin treatment arms than with comparator treatment in both studies.[16,17]

In type 2 diabetic patients inadequately controlled by diet, treatment with inhaled insulin resulted in better glycaemic control than with rosiglitazone.[18] After three months, the goal of HbA_{1c} <7% was achieved by 44% of patients in the inhaled insulin group compared with 8% in the rosiglitazone group. However, the study has been criticised for its relatively short duration, since rosiglitazone may take longer to become fully effective. Inhaled insulin resulted in more weight gain than rosiglitazone treatment (1.9 *vs* 0.8 kg), an observation possibly related to the higher rate of hypoglycaemia (0.7 *vs* 0.05 per patient-month) or faster achievement of good glycaemic control. In patients inadequately controlled by diet and a single oral agent (either metformin or a sulphonylurea derivative), addition of inhaled insulin was as good as an addition of a second oral agent from the alternative group.[19] Patients who were poorly controlled by two oral agents were found to benefit from switching to inhaled insulin monotherapy, but addition of inhaled insulin on top of oral therapy was even better.[20] An HbA_{1c} value below 7% was achieved by 32% of the patients in the combination group compared with 17 and 1% in the inhaled insulin and oral agent monotherapy groups, respectively. In insulin-treated type 2 diabetic patients, the combination of inhaled insulin at mealtimes and ultralente insulin subcutaneously resulted in similar improvement of glycaemic control as a subcutaneous regimen consisting of two to three injections of regular and NPH insulin.[21,22]

The daily dose of inhaled insulin averaged 15 mg after six weeks and 16.6 mg after 24 weeks of treatment. Weight gain did not appear to occur with inhaled insulin, whereas the subcutaneous regimen was associated with almost 1.5 kg increase in weight.[22]

AERx iDMS

The AERx iDMS delivery system was developed as a device for the pulmonary administration of liquid aerosols of insulin. The inhaler is breath activated and only releases the insulin when inspiratory flow is sufficient, in order to minimise intra-subject variability due to patient technique. The insulin is packaged in strips that contain an amount of insulin corresponding to approximately 1 unit subcutaneously. The bioavailability and pharmacological efficiency of the AERx iDMS system in type 1 diabetic patients were 12.9 and 12.7%, respectively.[23] In nondiabetic subjects, upper respiratory tract infections did not affect the pharmacological efficacy of AERx.[24] In a small, randomised, open-label study in 107 insulin-treated type 2 diabetic patients, the clinical effect of premeal use of AERx was compared with subcutaneous regular insulin, against a background of NPH insulin once daily.[25] After 12 weeks, HbA_{1c} fell by 0.69 and 0.77% in the inhaled insulin and subcutaneous insulin groups, respectively. Fasting blood glucose levels tended to be lower with inhaled insulin (7.04 *vs* 7.78 mmol/p, p=0.08), but prandial increments were similar. Patients in the inhaled insulin group received, or required, more contacts and more time per contact for instruction than the patients from the comparator group.

Human inhaled insulin powder

Advanced inhalation research developed large porous particles of low mass that consist of a biodegradable polymer matrix that contains fast-acting human insulin. Future developments might involve production of a sustained-release formulation. The capsules contain human inhaled insulin powder (HIIP) as a dry powder in two dose strengths of either 0.9 mg or 2.6 mg, equivalent to 2 or 6 units of subcutaneous insulin, respectively.[26] A preliminary study involving 137 type 1 diabetic patients reported that premeal use of this inhaled insulin in combination with glargine was clinically equivalent to a subcutaneous regimen of premeal regular or lispro insulin and glargine.[27] However, as this study was designed to show noninferiority of inhaled insulin, its efficacy to reach glycaemic targets was not tested.

Other products

Technosphere insulin is a dry-powder pulmonary insulin packaged in microparticles to which an absorption enhancer is added. The particles rapidly dissolve in the alveolar space to release insulin. The absorption of Technosphere insulin occurs faster and more efficiently than the other inhaled insulin products, with respect to time-to-peak insulin concentration (13 minutes), time-to-maximal effect (39 minutes), and bioavailability relative to subcutaneous (26%) and intravenous insulin (19%).[28] Clinical studies are awaited. Aerodose is a novel liquid pulmonary insulin with a relative bioavailability of 21% in type 2 diabetic patients,[29] yet its development has been halted. Other inhaled insulin formulations under development are ProMaxx, Kos insulin and Spiros.

SAFETY

Hypoglycaemia

Several studies have reported a slightly lower relative risk for any hypoglycaemic event with the use of inhaled *vs* subcutaneous insulin, ranging from 0.69 to 0.96, both in type 1 and type 2 diabetes.[16,22,25] These data are at odds with studies reporting a doubling of the incidence of severe hypoglycaemic events (6.5 *vs* 3.3 events per 100 patient-months)[17] and a higher incidence of nocturnal hypoglycaemia[27] in type 1 diabetic patients randomised to inhaled insulin compared with those randomised to subcutaneous treatment. A Cochrane systematic review on six randomised controlled trials concluded that, overall, there was no or little difference in hypoglycaemic risk between inhaled and subcutaneous insulin.[30]

Pulmonary adverse events

Concern has been raised that the alveolar deposition of insulin may have adverse pulmonary effects, because of insulin's vasodilator and growth promoting characteristics. To date, however, pulmonary oedema or malignant tumours have not been reported in association with inhaled insulin use. In general, inhaled insulin is well tolerated. The main adverse event reported by users of dry-powder inhaled insulin formulations is cough. In the trials with Exubera, 8 to 27% of patients on inhaled insulin *vs* 1.5 to 7% of patients on comparator treatment reported cough,[16-18,20,31] usually occurring directly following inhalation and characterised as mild to moderate. Shortness of breath was also more prevalent in the inhaled insulin groups than in the control groups. However, these adverse events rarely lead to discontinuation of treatment.[32] Neither cough nor shortness of breath was reported in excess by patients randomised to liquid inhaled insulin compared with subcutaneous insulin.[25]

Pulmonary function tests have revealed a slightly greater reduction in both forced expiratory volume in 1 second (FEV_1) and in monoxide diffusing capacity (DL_{CO}) in patients allocated to inhaled insulin treatment than in those of the comparator groups. The differences occur in the first weeks, are small and not progressive. In a study among type 2 diabetic patients, the difference in

FEV_1 and DL_{CO} between inhaled insulin treatment and control treatment decreased gradually between week 24 and 104, and was no longer discernible 12 weeks after discontinuation.[33] In addition, annualised declines of FEV_1 and DL_{CO} during a four-year extension study did not appear to continue in 159 type 1 and type 2 diabetic patients who had chosen to continue inhalation therapy or to switch from comparator treatment after a randomised clinical trial.[34] These data do not exclude long-term pulmonary side effects of inhaled insulin, since patients at high risk for pulmonary disease (e.g. smokers) have been excluded from participation in clinical studies. Moreover, pulmonary function appears to deteriorate with worsening glycaemic control[35] and structural pulmonary abnormalities have been suggested to parallel the development of classical microvascular complications in diabetes, both of which raise concern with respect to inhaled insulin treatment.[36] Clearly, much longer follow-up data are required to establish pulmonary safety for a product destined to be inhaled for a lifetime of diabetes.

Insulin antibody response

In all studies, inhaled insulin was found to produce larger insulin antibody responses, mainly of IgG class, than subcutaneous insulin, irrespective of formulation. Pooled data from studies on Exubera revealed a relationship with prior therapeutic insulin exposure. Median antibody responses increased from 3 to 31% in patients with type 1 diabetes, and from less than 3% to 13 and 6% in insulin-treated and insulin-naive type 2 diabetic patients, respectively.[37] The peak in antibody responses was observed after 6 to 12 months of treatment and then stabilised in all groups. Use of AERx or other inhaled insulin products was associated with similar excess in insulin antibody responses.[25] The clinical relevance of this observation has not yet been clarified. So far, no relation has been found between presence of insulin antibodies and insulin dose requirements, fasting blood glucose levels, glycaemic control, hypoglycaemia incidence, or adverse events.[37]

PATIENT PREFERENCES

In terms of quality of life and treatment satisfaction, the development of smaller and sharper needles and pen-injector systems may have benefited patients at least as much as the biochemical advances in the production of injectable insulins. Nevertheless, many patients welcome a noninvasive alternative. Type 2 diabetic patients failing on oral hypoglycaemic agents (mean HbA_{1c} 9.1%) were almost three times as likely to choose (additional) insulin therapy if inhaled insulin would have been available than if they could only select standard insulin therapy.[38] In randomised trials that included assessment of treatment satisfaction, patients allocated to inhaled insulin ended up being more satisfied (with insulin treatment) than patients allocated to subcutaneous insulin.[15-17,22] After successful completion of one of two 12-week randomised controlled trials, 85% of (type 1 and type 2 diabetic) patients randomised to inhaled insulin chose to continue treatment and 75% of patients who had received subcutaneous insulin chose to switch to inhaled insulin. After one year, treatment satisfaction was universally greater in patients treated with inhaled insulin than in patients treated subcutaneously, irrespective of their initial treatment allocation in the parent studies.[39] It was concluded that diabetic patients prefer inhaled insulin to subcutaneous insulin. However, interpretation of the data is critical when the comparator treatment consists of continuation of existing therapy. This is illustrated by studies showing that the magnitude of treatment satisfaction is determined mainly by the level of (improvement in) glycaemic control, whereas this parameter did not differ between inhalation insulin and comparator treatment arms.[40,41] An explanation for this seemingly paradoxical phenomenon is that patients allocated to inhalation insulin might have been tempted to attribute glycaemic improvement to the novel experimental agent (possibly enhanced by enthusiasm from their healthcare providers), whereas those allocated to continuation of subcutaneous insulin might have attributed improvement to a study effect. In turn, it could be speculated that increased motivation to comply with dietary instructions explained the absence of weight gain and the lower fasting plasma glucose levels in the inhaled insulin groups.

FINANCIAL ASPECTS

At the moment, none of the companies have disclosed the price of their product. Due to the high insulin content and costs of development, it is anticipated that inhaled insulin will cost considerably more than currently available subcutaneous insulin preparations, including insulin analogues. Moreover, extra costs are to be expected due to the need for pulmonary function monitoring. The supposed greater convenience and acceptability of inhaled insulin compared with subcutaneous insulin has been suggested to enhance willingness in type 2 diabetic patients to use insulin for optimisation of glycaemic control, thereby reducing health care cost.[38] However, a study on cost effectiveness of inhaled insulin has not yet been performed. The Real World Trial, which aims to investigate the effect of introducing inhaled insulin to clinical practice on health benefit and is due to report in 2007, may provide some answers on this issue.[42] If inhaled insulin turns out to be the blockbuster it is assumed (or hoped) to become, a costly boost of the production capacity of therapeutic insulin is likely to be required.

CONCLUSION AND PERSPECTIVES

Inhaled insulin is the first noninvasive alternative to subcutaneous insulin administration that is to be marketed this year. Despite the relatively low bioavailability of most products, pulmonary administration of insulin provides clinically effective plasma insulin levels and sufficient blood glucose lowering. Its pharmacological profile resembles that of subcutaneous immediate-acting insulin analogues, making inhaled insulin suitable for premeal administration. Clinical studies in type 1 and type 2 diabetic subjects indicate equivalence between inhaled insulin-based regimens and subcutaneous insulin-based regimens with respect to glycaemic control and incidence of hypoglycaemic events, provided that basal insulin requirements are met. However, comparator treatment often involved a suboptimal regimen, whereas inhaled insulin was given in a basal-bolus regimen, making comparisons difficult. Despite its pharmacological profile, a randomised controlled trial comparing inhaled insulin with immediate-acting analogues has not yet been published. Inhaled insulin monotherapy may be as good as or better than oral agents in achieving glycaemic targets in type 2 diabetic patients who fail on diet or single-agent oral therapy. The combination of the two is better than either treatment alone.

Long-term safety remains an issue of concern. Although the absence of clinically relevant pulmonary adverse events with use of inhaled insulin is encouraging, data were obtained over relatively short follow-up and in patients without risk factors for pulmonary disease. Smokers and patients with obstructive lung disease have not been enrolled in inhaled insulin studies. More and longer-term studies are required. These may also disentangle the immunogenicity of inhaled insulin, for instance to determine whether insulin antibodies are able to cross the placenta.

In the absence of a clear clinical benefit on subcutaneous insulin, there is currently no indication for inhaled insulin treatment in patients with type 1 or insulin requiring type 2 diabetes mellitus. Nevertheless, it is well known that the switch to insulin therapy is often delayed in type 2 diabetic patients poorly controlled by oral treatment and lifestyle changes alone, despite the obvious advances with respect to glycaemic control and risk of complications. High acceptance of inhaled insulin might encourage these patients to switch to insulin therapy at an earlier stage, but this needs to be confirmed in clinical practice. In addition, the availability of inhaled insulin may benefit the management of selected patient groups, such as those with severe needle phobias, patients with recurrent local complications of subcutaneous insulin (such as skin infections or skin contact allergies), and patients with dermatological ailments or severe lipodystrophia for whom finding a suitable injection spot may be difficult. These patients should not smoke (in the past six months), have ongoing pulmonary disease or reduced pulmonary function, be pregnant, or be younger than 18 years of age. Caution should be exercised in patients with microvascular complications and in those with poor glycaemic control. Whether inhaled insulin will be cost-effective remains an important, yet unresolved, issue.

NOTE

B.E. de Galan and C.J. Tack have participated in a phase II clinical trial with Technosphere insulin. R.J. Heine is a member of the International Advisory Board of Pfizer Inc.

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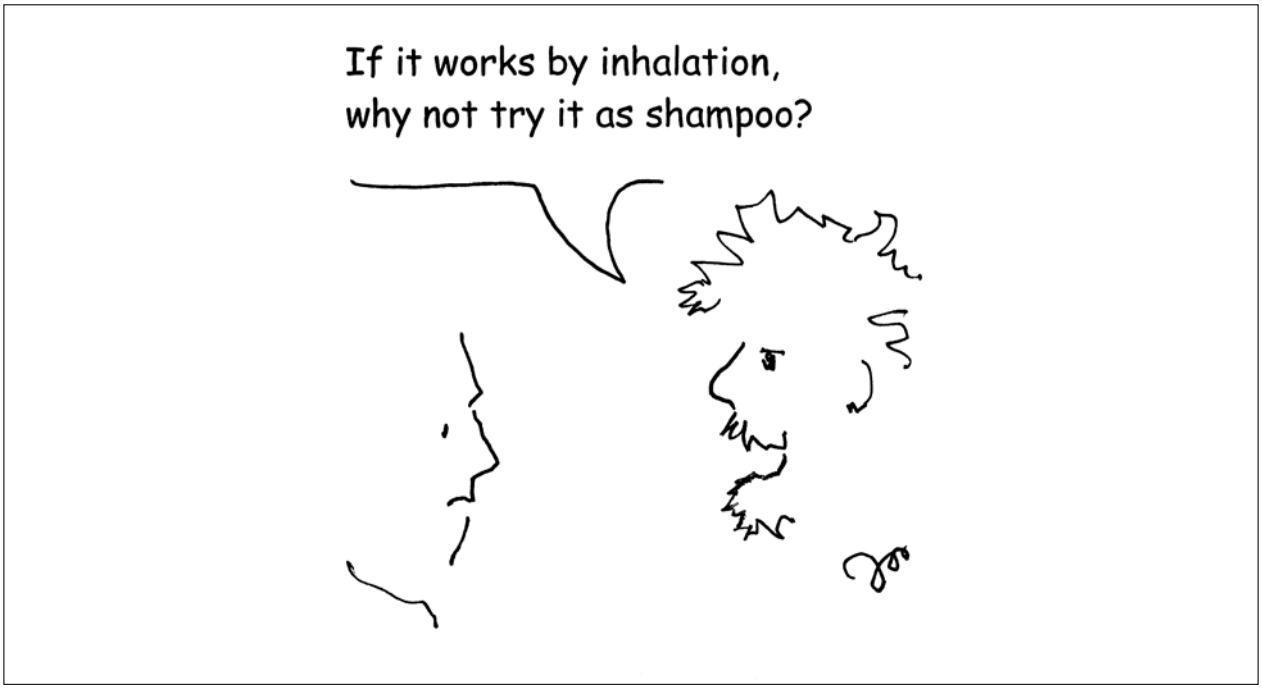

De Galan, et al. Treatment with inhaled insulin.

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REVIEW

Oxybutynin: dry days for patients with hyperhidrosis

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ABSTRACT

We report the case of a 56-year-old postmenopausal woman who was referred to our Endocrinology Outpatient Clinic because of severe hyperhidrosis. She had a four-year history of excessive sweating of her face and upper body. On presentation no sweating could be documented. Physical examination was also unremarkable. It appeared that five days earlier her general practitioner had prescribed oxybutynin for urge incontinence and this accidentally cured her hyperhidrosis. She was diagnosed with idiopathic hyperhidrosis. We advised her to continue the oxybutynin and six months later, she was still symptom-free. Oral anticholinergic drugs are known to be effective for hyperhidrosis, but only anecdotal reports on oxybutynin can be found in the literature. Oxybutynin is not approved for hyperhidrosis, explaining the unfamiliarity with this medicine. This case shows that oxybutynin can be a very effective and simple treatment with only mild side effects. Therefore, oxybutynin merits consideration in patients with idiopathic hyperhidrosis. This report includes a concise review of the causes and treatment options of hyperhidrosis.

KEYWORDS

Anticholinergics, hyperhidrosis, oxybutynin, sweating

Table 1. *Causes of hyperhidrosis*

Generalised
Menopausal
Endocrine diseases: hyperthyroidism, carcinoid syndrome, pheochromocytoma, mastocytosis, diabetes mellitus, hypoglycaemia, acromegaly
Serotonin syndrome
Chronic infections: e.g. endocarditis, tuberculosis, HIV infection
Malignancy: lymphoma, bronchial carcinoma with compression of the sympathetic chain
Neurological: brain damage, spinal cord injuries, autonomic dysreflexia, Parkinson's disease, Shapiro's syndrome
Drug-induced: antidepressants, antipyretics, antimigraine drugs, cholinergic agonists, GnRH agonists, sympathomimetic agents, β-blockers, cyclosporine and many others
Focal
Idiopathic palmar, plantar, axillary and/or facial hyperhidrosis
Hexsel's hyperhidrosis: inguinal hyperhidrosis
Localised unilateral hyperhidrosis (LUH): restricted to an area smaller than 10 x 10 cm on the forearm or forehead, unknown pathogenesis
Ross' syndrome: a progressive segmental anhidrosis of the trunk with a compensatory band of excessive hyperhidrosis
Frey's syndrome (gustatory sweating): preauricular hyperhidrosis and flushing in response to eating, a common complication after parotid gland surgery
Harlequin syndrome: episodic unilateral facial flushing and sweating

INTRODUCTION

Hyperhidrosis, or excessive sweating beyond physiological needs, is not a rare problem (prevalence 1%).[1] Not only endocrinologists, but particularly general practitioners, internists and dermatologists are confronted with this disorder. Hyperhidrosis may be either focal (localised) or generalised (*table 1*).[2] According to its aetiology, it may be primary or secondary. Primary hyperhidrosis is usually idiopathic and focal, affecting the palms, axillae, plantar surfaces, face and neck. The condition is frequently brought on by emotional response. In addition, there is evidence of a genetic predisposition. Studies are currently being performed to identify the responsible gene(s). Secondary hyperhidrosis tends to be generalised and is typically associated with endocrine diseases (including hyperthyroidism, diabetes, pheochromocytoma, carcinoid,

systemic mastocytosis) but also occurs with malignancy and neurological diseases. In addition, hyperhidrosis can be a side effect of many drugs. Secondary hyperhidrosis is usually caused by a resetting of the sweat centre in the hypothalamus. Besides primary and secondary hyperhidrosis, several rare forms of focal hyperhidrosis occur in association with specific syndromes: localised unilateral hyperhidrosis (LUH), Ross' syndrome, Frey's syndrome and Harlequin syndrome (*table 1*).

Even today, hyperhidrosis is often misconceived to be an untreatable disorder. For idiopathic hyperhidrosis, several proven effective treatments are available: local treatment with aluminium (hydro)chloride, local resection of sweat glands, iontophoresis, botulinum toxin, and endoscopic sympathectomy (*table 2*).[3-6] We describe a patient who was successfully treated with oxybutynin.

Table 2. *Current therapeutic options for hyperhidrosis (in step-wise order)*

Generalised hyperhidrosis
Treat the underlying disorder, if present
Hormone-replacement therapy in menopausal hyperhidrosis
Anticholinergics
Focal hyperhidrosis
Treat the underlying disorder, if present
Local antiperspirants: aluminium chloride 20%, aluminium hydrochloride 15%
Anticholinergics
Iontophoresis
Botulinum toxin
Thoracoscopic sympathectomy
Local excision of skin and subcutis with sweat glands

CASE REPORT

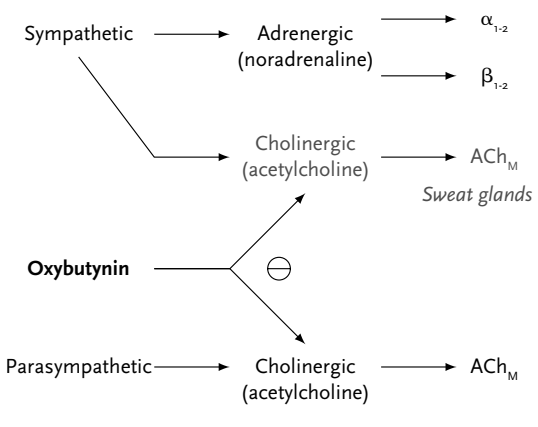
A 56-year-old woman was referred by her general practitioner to our endocrinology outpatient clinic because of a four-year history of excessive sweating of her face and upper body. She had to wash and change clothes many times a day and could not leave the house without towels. The palms and soles remained dry. She had no flushing. Her last menstruation was three years ago. Her general practitioner (GP) considered climacterial hyperhidrosis, but she refused hormone-replacement therapy because her mother had had breast cancer. The sweating was continuous, had no diurnal variation and was not related to social situations. However, on presentation no sweating could be documented. Further extensive physical examination was also unremarkable. It appeared that the GP had started oxybutynin (2.5 mg three times daily) five days earlier because of urge incontinence. Since then, she had had no more complaints of excessive sweating. Underlying causes of hyperhidrosis, e.g. endocrinopathies, infections and malignancy, were excluded by blood testing and a chest X-ray. The diagnosis of idiopathic hyperhidrosis was made. We advised her to continue taking the oxybutynin. Six months later, she was still symptom-free.

DISCUSSION

Comment on the case report

This cases illustrates that hyperhidrosis is a socially embarrassing disorder with a profound effect on the patient's quality of life. Furthermore, it is striking how long hyperhidrosis usually exists before patients consult a doctor. This patient responded remarkably well to low-dose oxybutynin (brand name Dridase, named after its effect: 'dry days'). Oxybutynin is a parasympathicolytic drug with a spasmolytic effect on the detrusor muscle of the bladder due to antagonism of the muscarine receptors. Although the sweat glands are innervated by sympathetic postganglionic nerve fibres, they use acetylcholine, the neurotransmitter that is generally used exclusively by parasympathetic nerves (*figure 1*). Thus, the anticholinergic effect of oxybutynin is responsible for its effectiveness against excessive sweating.[7] Understanding of the mechanism of sweating and the first use of anticholinergics dates back to the 19th century, when it was accidentally discovered that elixirs from atropine plants improved hyperhidrosis.[8] Although today the effectiveness of oral anticholinergics in hyperhidrosis is commonly known, experience with oxybutynin in hyperhidrosis is limited: only anecdotal reports exist in the literature.[9] Oxybutynin is not approved for hyperhidrosis in Europe, explaining the unfamiliarity with this medicine. None of the anticholinergic drugs available in Europe are registered for use in hyperhidrosis. In the USA, glycopyrrolate

Figure 1. *Overview of the autonomous nervous system and effect of oxybutynin on the eccrine sweat glands*



(Robinul) is available for this indication. The result in the above-mentioned patient suggests that oxybutynin, primarily indicated for urge incontinence, should be considered as a useful alternative. Potential side effects include dry mouth, constipation, nausea, blurred vision and urinary retention. The side effects of oxybutynin are mild as compared with other anticholinergics such as atropine. The statement that use of anticholinergics should not be recommended because of unacceptable side effects at dosages required for efficacy cannot be confirmed by our experience with this patient. During the six months' follow-up, dose increment was not necessary to maintain effectiveness. However, long-term use, although probably safe, is a major drawback for many patients and should not be recommended.[10] Because of its rapid resorption (T_{max} <1 hour), oxybutynin would also be suitable for use 'on demand', for example in specific social situations that provoke hyperhidrosis. A placebo-controlled clinical trial should be the next step to study the effectiveness and side effects of oxybutynin in a large group of patients with hyperhidrosis.

Current treatment options in hyperhidrosis: overview of the literature

The initial treatment of focal idiopathic hyperhidrosis[3-6] consists of local application of aluminium (hydro)chloride. If unsuccessful, an oral anticholinergic can be tried.

Axillary hyperhidrosis can be treated with en bloc excision of skin and subcutaneous tissue containing the sweat glands. However, this procedure is rarely performed because it is invasive and has a significant failure rate.

Iontophoresis is an effective treatment for palmoplantar hyperhidrosis. Iontophoresis involves immersion of the palms and/or soles in small basins filled with warm tap water and the use of a D/C generator that leads a low intensity electrical current (15 mA) through the water.[3,5] Charged ions are driven into the skin and temporarily disrupt the function of the sweat glands. Various devices are commercially available for home use. Treatment is time-consuming (multiple sessions are required per week), but safe, simple and effective in 85% of cases. Adding anticholinergics to the water can increase the effect.

Intradermal injections with botulinum toxin can by applied in axillary and palmar hyperhidrosis. Botulinum toxin inhibits the release of acetylcholine at the cholinergic synapse and binds to acetylcholine receptors at the synaptic end-plate.[2,7] The effect lasts for three to six months. Botulinum toxin is the first-line treatment of Frey's syndrome.

Severe therapy-resistant axillary or palmar hyperhidrosis can be treated surgically with an endoscopic thoracic sympathectomy.[11] This involves endoscopic removal of the sympathetic ganglia at Th2 for facial hyperhidrosis, Th2-3 for palmar hyperhidrosis and Th2-4 for axillary hyperhidrosis. The treatment is very effective (sweat control in 75 to 95% of patients) but is often complicated by compensatory sweating of the trunk and legs.[12,13]

In idiopathic generalised hyperhidrosis, a low-dose oral anticholinergic is the best available treatment. Other oral or systemic medications that have been tried include β-blockers, sedatives, antidepressants, clonidine, calcium antagonists and NSAIDs, but none have proven to be effective.

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ORIGINAL ARTICLE

Validation of a new, commercially available dry rapid urease test for the diagnosis of *Helicobacter pylori* infection in gastric biopsies

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ABSTRACT

Background: To compare the accuracy and reaction time of a new dry rapid urease test (GUT test) with the CLO test and an independent gold standard in the diagnosis of *Helicobacter pylori* infection. To determine whether this new test can replace the CLO test in routine clinical practice.

Methods: We included consecutive patients in whom normal-sized gastric biopsies were taken in routine practice. Six antral and three corpus biopsies were taken for determination of *H. pylori* infection. Results of the GUT test were monitored after 15, 60 and 120 minutes of incubation. Results were compared with the standard CLO test and an independent gold standard (bacterial culture and histology). The results of the CLO test were also compared with the gold standard.

Results: 116 patients were recruited in the study: 60 were males and 56 females. The mean age was 59.3 years (range 14-89 years). Compared with the CLO test, the GUT test had a sensitivity of 76.7% and a specificity of 100% in 15 minutes. After 60 minutes the sensitivity of the GUT test increased to 95.3%, the specificity remained 100%. All positive results of the GUT test occurred before 60 minutes of incubation. Compared with the gold standard, the GUT test had a sensitivity and specificity of 97.4 and 96.1% respectively. The CLO test had a sensitivity of 97.4% and a specificity of 93.5%, when compared with the gold standard.

Conclusion: The GUT test appeared to be a good and reliable alternative for the widely used CLO test in diagnosing *H. pylori* infection. The GUT test results were not yet reliable after 15 minutes, but all positive results occurred before 60 minutes of incubation. The test can best be read 60 to 120 minutes after endoscopy.

KEYWORDS:

Diagnosis, dry rapid urease test, GUT test, *H. pylori*

INTRODUCTION

Helicobacter pylori is a spiral-shaped Gram-positive bacterium which produces the enzyme urease. These bacteria are found in human gastric mucosa, wherever this is situated in the human body. *H. pylori* bacteria are usually found under the mucus layer in the gastric pits and in close apposition to gastric epithelial cells.[1] *H. pylori* infection causes chronic active gastritis in the antrum (antral gastritis), the corpus (corpus gastritis) or in both (pangastritis). It is a major aetiological factor in peptic ulcer disease.[1] Haemorrhage and perforation are the most frequent complications of peptic ulcer disease and are associated with substantial morbidity, mortality and health care costs. Patients with recurrent haemorrhage, particularly the chronically ill and elderly, have excessive morbidity and mortality.[2] Peptic ulcer disease can be cured by eradicating *H. pylori* so that complications no longer occur.[1] *H. pylori* infection is also a major aetiological factor in gastric cancer and B cell lymphoma.[1,3-5]

H. pylori infection can be diagnosed by biopsy-based tests but these require an endoscopy. There are also some noninvasive tests such as serology, faecal antigen testing and urea breath testing. However, no single test is currently available that can provide the definite diagnosis by itself. Due to this lack of a true gold standard, biopsy-based tests are still considered to be the reference method for diagnosing *H. pylori* infection and monitoring eradication treatment.[6] The most widely used biopsy-based tests are histology, culture and rapid urease tests.

We have previously shown that a combination of these three tests is a very reliable method for the diagnosis of *H. pylori* infection.[7] With this combination a calculated sensitivity of 98.3% and a specificity of 99.7% can be reached. This translated into a positive predictive value (PPV) of 99.6% and a negative predictive value (NPV) of 98.9% in 869 patients.[7]

Biopsy urease tests can determine the presence or absence of urease activity in a gastric biopsy. This enzyme is only produced by *H. pylori*. Presence of urease activity in a biopsy can therefore be considered as proof of the presence of this infection.[8] A biopsy urease test container carries urea and the biopsy is immersed in the fluid or gel. If *H. pylori* is present the urease activity will break down urea, thereby generating ammonia. The resulting elevation of pH (decrease in acidity) can be detected by an indicator, usually phenol red, and this will change the colour from yellow to red.[9] Rapid urease tests have the advantage that they are not operator dependent, they have a high reproducibility worldwide and they are cheaper than culture or histology.[8]

The CLO test is the most widely used commercial biopsy urease test. We have a wide experience with this test. In 468 pretreatment endoscopies the CLO test had a sensitivity, specificity, PPV, NPV and accuracy of 91.4, 99.4, 99.7, 85 and 94% respectively. In 244 post-treatment endoscopies this was 93.3 100, 100, 99.1 and 99.2% respectively.[8]

There are a few well-validated wet rapid urease tests commercially available: CLO test,[10-17] HUT test,[15] Helicocheck[18] and HPfast[17] and also one dry rapid urease test: PyloriTek.[10,12,14,16-20] In order to save costs, urease tests can also be produced locally by the hospital pharmacist.[21,22]

The new and commercially available gastroscopic urease test (GUT test) is a cheap alternative for the currently available tests.

The aim of this study was to compare the accuracy and reaction time of the newly available GUT test with the CLO test and with the gold standard in the diagnosis of *H. pylori* infection. We wanted to determine whether this new test can reliably replace the CLO test in routine clinical practice.

MATERIALS AND METHODS

In this study we included consecutive patients in whom normal-sized biopsies for determination of *H. pylori* status were taken by three experienced endoscopists in a Dutch community hospital. The use of acid-suppression therapy was allowed. A standard biopsy protocol was used for *Helicobacter* diagnosis at all times. At baseline, gender and age were recorded. In patients being examined for *H. pylori* infection, six antral and three corpus biopsies were taken. One antral biopsy was sent for bacterial culture. Two antral and two corpus biopsies were used for histological examination. One antral and one corpus biopsy were used for two separate CLO tests and two antral biopsies were used for the GUT test. Test outcome for each method was assessed independently from the other test results: culture results by a microbiologist, histology results by a pathologist and urease test results by the endoscopist. Because the GUT test biopsies were only taken from the antrum of the stomach, their results were compared with the antral CLO test results and the antral histology and culture results. In this way we can make a good comparison of the different methods and the results are not biased by patients in whom *H. pylori* is only present in antrum and not the corpus or *vice versa*.[13,23]

Antral histology and antral culture together were considered the independent gold standard for the diagnosis of *H. pylori* infection in this study. A positive diagnosis of infection was made when one of these two tests was positive or when both these tests were positive.

Culture

One biopsy specimen for bacterial culture was placed in 1 ml of thioglycolate broth and transported to the microbiological laboratory within six hours of upper gastrointestinal endoscopy. Culture was done with Belo-Horizonte medium containing brain-heart infusion agar (35 g/ml), sheep blood (10%), vancomycin (10 mg/l), trimethoprim lactate (5 mg/l), cefsoludin (5 mg/l), and amphotericin (5 mg/l). The plates were incubated microaerobically at 36°C for seven days. Identification was confirmed by Gram staining, catalase, oxidase activity, and hydrolysis.

Histology

For histological examination, two biopsy specimens were fixed in neutral buffered 4% formaldehyde. *H. pylori* identification was performed on Giemsa-stained sections of paraffin-embedded tissue.

CLO test

To measure urease activity in our biopsy we performed the CLO test (Delta West, Bentley, Western Australia). One antral and one corpus biopsy specimen were placed in two separate plastic cups of two CLO tests, both containing a urea agar gel with phenol red buffer. After immersing the biopsy in the test it was kept at body temperature in the pocket of the endoscopist for up to ten hours to speed up the chemical reaction. The CLO test was read after 24 hours.

GUT test

Two extra antral biopsy specimens were used in the GUT test (Lencomm Trade International, Warschau, Poland/ Lansmedical, Huissen, the Netherlands) for this study. The label was peeled off, exposing the test well which is a dry filter paper. With a sterile needle, the specimens were removed from the biopsy forceps and placed into this well. After resealing the test the label was pressed over the test dot with

the finger to squeeze the tissue juice out of the specimens and this is absorbed by the filter paper. Results were monitored at room temperature after 15, 60 and 120 minutes. When urease was present in the tissue, an expanding magenta colour zone was noted around the biopsy.

RESULTS

Altogether, 116 patients were recruited in the study. Of these patients, 61 were males and 56 were females. The mean age was 59.3 years with a range of 14 to 89 (*table 1*). The diagnosis of *H. pylori* infection was made, according to the gold standard, in 39 patients, while the other 77 patients were regarded as negative.

Interpretation of the GUT test appeared to be easy, we had no equivocal results. Compared with the CLO test, the GUT test had a sensitivity of 76.7% (95% CI: 63.9 to 89.6%) and a specificity of 100% (95% CI: 98.4 to 100%) in 15 minutes. After 60 minutes the sensitivity of the GUT test increased to 95.3% (95% CI: 88.9 to 100%), the specificity remained at 100% (95% CI: 98.4 to 100%). After 60 minutes incubation no additional positives were found. The results after 120 minutes were therefore the same as after 60 minutes.

Compared with the gold standard the GUT test had a sensitivity of 79.4% (95% CI: 66.6 to 92.4%) and a specificity of 97.4% (95% CI: 93.8 to 100%) after 15 minutes incubation. After 60 minutes incubation the sensitivity increased to 97.4% (95% CI: 92.4 to 100%), the specificity became 96.1% (95% CI: 91.7 to 100%). This remained the same after 120 minutes.

When compared with the same gold standard, the CLO test had a sensitivity of 97.4% (95% CI: 92.4 to 100%) and a specificity of 93.5% (95% CI: 87.9 to 99.1%).

The results of the tests are presented in *table 2*.

Table 1. *Patient characteristics*

N	116
Male : female	60 : 56
Mean age	59.3 years
Age range	14-89

DISCUSSION

The GUT test appeared to be a good and reliable alternative for the widely used CLO test in diagnosing *H. pylori* infection.

The GUT test results were not yet reliable after just 15 minutes. The test slide only changed colour within a time span of 15 minutes when a high bacterial load was present. Our results demonstrate that there are still many false-negative results after 15 minutes. All positive test results (colour change) occurred between 15 and 60 minutes. No additional positives were found thereafter. This indicates that the test can best be read after at least 60 minutes. Results at 60 and 120 minutes were similar, but we did not investigate the stability of the colour change thereafter. We do not know if the test can still be trusted if it is read longer than 120 minutes after the procedure. This information, however, might be important in a situation when the test is forgotten and left overnight.

Biopsy rapid urease testing is the most simple and rapid method for identifying *H. pylori* infection in endoscopic practice.[6,8] Moreover, these tests are not dependent on the experience and accuracy of individual laboratories as is the case for histological examinations or culture. False-positive rapid urease tests are rare.[10-17] When patients salivate excessively or have reflux of alkaline bile into the stomach, this liquid may contaminate a small gastric biopsy specimen such that the resulting surface pH is >6.0. In theory, this situation could cause a weak positive reaction in some rapid urease tests. Similarly, patients taking a proton pump inhibitor chronically may develop achlorhydria with subsequent superficial colonisation of the gastric mucus layer with urease-producing organisms (e.g., *Proteus mirabilis* or *Klebsiella*). These organisms can give a false-positive urease test after 24 hours of inoculation but generally tests are still negative when the test is read one hour after biopsy insertion.[9]

Other authors have shown that acid-suppressing medication prolongs the time to positivity for the rapid urease tests.[24] Use of proton pump inhibitors increases the numbers of false-negative tests. Two possible mechanisms by which acid-suppressing medication delays positivity in the CLO test are known. First, the medication may directly inhibit

Table 2. *The results of the GUT test compared with those of the CLO test and the gold standard*

		CLO test		Gold standard	
		Positive	**Negative**	**Positive**	**Negative**
15 minutes incubation	GUT positive	33	0	31	2
	GUT negative	10	73	8	75
60 minutes incubation	GUT positive	41	0	38	3
	GUT negative	2	73	1	74
120 minutes incubation	GUT positive	41	0	38	3
	GUT negative	2	73	1	74

H. pylori urease. Secondly, CLO test positivity may be delayed due to changing patterns of *H. pylori* colonisation after acid suppression. *H. pylori* often only resides in the corpus during long-term use of proton pump inhibitors and can therefore not be detected in antral biopsies.[24]

The presence of blood may adversely affect the performance of all biopsy urease tests. This is explained by the buffering effect of serum albumin on the pH indicator, rather than by a direct inhibition of the urease activity.[25]

The GUT test gives a very distinct colour change in all cases. A positive reaction is noted when the yellow ring in the test well turns a distinct magenta, which is clearly distinguishable from contamination by blood. In the CLO test blood around the biopsy sample may give an initial false impression of a positive test. Therefore, the CLO test can only be interpreted as positive with confidence when the colour changes the total volume of the agar gel.[26]

The advantage of this new GUT test is that the results are available faster than the results of the CLO test (after one hour and 24 hours respectively). Another economic advantage is that the GUT test is cheaper than the CLO test. The CLO test has an incubation period of 24 hours,[24] requires refrigeration for storage and needs to be warmed to room temperature prior to use. Another advantage of the GUT test is therefore that it does not require any special storage conditions. It can be stored at room temperature in the endoscopy suite and is therefore readily available.

A disadvantage of the GUT test is that so far it has only been validated with the use of two biopsies in one test slide; taking an extra biopsy is time-consuming. In contrast the CLO test has been widely validated with only one biopsy in the test slide. Some authors, however, have also recommended putting two biopsies in one CLO test slide. Adding a second biopsy in the same agar cup speeds up the reaction and may partly eliminate the problem of sampling error. Theoretically this may improve sensitivity.[6] Some found *H. pylori* in a patchy distribution throughout the stomach.[13,23] The most reliable diagnosis of infection is therefore achieved by testing multiple sites.[6,27] *H. pylori* is not present in intestinal metaplasia and this may indeed be a reason for missing the diagnosis if only a site of metaplasia is sampled. In the GUT test we used two biopsies in one test slide. This may also have improved the sensitivity of the GUT test. Further research is therefore needed with one biopsy in the GUT test. Until this research has been done users of the GUT test need to add two biopsies in order to know that they have a reliable test.

Two possible explanations can be given for the more rapid reaction time of the GUT test. First the biopsy tissue is squeezed with the finger as recommended by the manufacturer. By doing this the tissue 'juice' and the urease enzyme reacts with the test substrate. Second, the urease enzyme can be absorbed very quickly because of the presence of the dry filter paper ring around the test well, causing a rapid colour change. In contrast the CLO test depends on the slower diffusion of urease into the agar gel which contains the urea substrate. In the CLO test the speed of the reaction also depends on the way the biopsy is placed in the agar gel.[26] If the CLO test is used properly the biopsy needs to be immersed completely into the gel with a sterile needle. However, in real life the biopsy is sometimes only put on top of the agar gel and the lower contact surface delays the colour change.

The GUT test has been validated once before by Said *et al.*[26] They compared the GUT test, which in their study is called the Pronto Dry, with the CLO test in 208 patients. In this study the results for both the Pronto Dry and the CLO test were completely concordant. The Pronto Dry had a sensitivity, specificity, PPV, NPV and diagnostic accuracy of 98.1, 100, 100, 98.1 and 99%, respectively. The Pronto Dry showed a faster reaction time to positive compared with the CLO test. With Pronto Dry 96.2% of all positive reactions occurred before 30 minutes *vs* 70.8% for the CLO test. Pronto Dry had a 100% positive reaction time by 55 minutes *vs* 83% for the CLO test.

Tseng *et al.*[28] have investigated the accuracy and positive reaction time of two new rapid urease tests (Pronto Dry and Hp One) in 49 patients. In their study the sensitivities, specificities, PPVs and NPVs of the three rapid urease tests were not significantly different.

Our results are therefore in agreement with these earlier validation studies.

CONCLUSION

From our study we conclude that the GUT test with two gastric biopsies is highly accurate for the diagnosis of *H. pylori* infection. Compared with the CLO test, the GUT test gives the endoscopist a more rapid test result and it is much cheaper. Because it can be stored at room temperature in the endoscopy room it is always easily available. The GUT test results were not yet reliable after 15 minutes. However, all positive results occurred before 60 minutes of incubation. Test results did not change between 60 and 120 minutes. This indicates that the test can best be read 60 to 120 minutes after endoscopy.

Based on our data we believe that this is a reliable, very attractive and affordable biopsy urease test for the diagnosis of *H. pylori* infection.

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ORIGINAL ARTICLE

HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre

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ABSTRACT

The number of patients taking HMG-CoA-reductase inhibitors for hypercholesterolaemia is growing rapidly. Treatment with HMG-CoA-reductase inhibitors significantly reduces the risk of cardiovascular morbidity and mortality, but may rarely cause serious adverse drug reactions (ADRs). The most serious ADRs of HMG-CoA-reductase inhibitors are musculoskeletal symptoms including myopathy and myositis, (life-threatening) rhabdomyolysis and liver failure. Furthermore, peripheral neuropathy might also occur, especially after long-term use of HMG-CoA-reductase inhibitors. Because of the severity and the relative rarity of HMG-CoA-reductase-induced neuropathy, the Netherlands Pharmacovigilance Centre Lareb has analysed its database of reported ADRs for reports concerning neuropathy associated with the use of HMG-CoA-reductase inhibitors. Until June 2005, Lareb received 17 reports of neuropathy, peripheral neuropathy and polyneuropathy and in addition two reports of aggravation of existing polyneuropathy associated with the use of HMG-CoA-reductase inhibitors. The associations neuropathy, peripheral neuropathy and polyneuropathy and the use of HMG-CoA-reductase inhibitors are statistically significantly more often reported to Lareb. The average time to onset supports conclusions of previous studies and case reports that especially long-term exposure increases the risk for peripheral neuropathy. Considering the increasing number of patients taking HMG-CoA-reductase inhibitors, health care professionals should be aware of the possible role of these drugs in neuropathy.

KEYWORDS

HMG-CoA-reductase inhibitor, hypercholesterolaemia, neuropathy

INTRODUCTION

A rapidly growing number of patients are taking hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA)-reductase inhibitors to reduce cholesterol levels in the framework of the primary and secondary prevention of atherosclerosis. Furthermore, HMG-CoA-reductase inhibitors reduce the risk of stroke and peripheral vascular disorders.[1] The Heart Protection Study showed a significant reduction in the risk of cardiovascular morbidity and mortality after treatment with HMG-CoA-reductase inhibitors. Death due to any vascular cause was reduced by 17% ($p<0.0001$).[2]
Besides their efficacy, HMG-CoA-reductase inhibitors can also produce a variety of adverse drug reactions (ADRs). However, clinically significant ADRs are rare and discontinuation due to ADRs varies from only 1.0 to 4.8%.[1] The most serious ADRs are musculoskeletal symptoms including myopathy and myositis, (life-threatening) rhabdomyolysis,[3,4] and liver failure.[1] Elevation of transaminase levels may occur in 1 to 3% of the patients taking HMG-CoA-reductase inhibitors.[5] Post-marketing studies and case reports suggest that HMG-CoA-reductase inhibitors are also associated with peripheral neuropathy,[6-10] for which the risk significantly increases after long-term use.[6]

Peripheral neuropathy

Peripheral neuropathy is a common term used to define disorders of the peripheral nervous system. The clinical symptoms of peripheral neuropathy may vary widely and include symptoms as paraesthesia or hyperaesthesia of the extremities, sensory loss, muscle weakness, atrophy and autonomic symptoms.[11,12] Electrodiagnostic investigations, including nerve conduction studies and needle electromyography, may be necessary for accurate diagnosis of peripheral neuropathy.[12]

Drug-induced neuropathy is in general characterised by degeneration of the axonal nerve.[8,13] However chronic axonal polyneuropathy has many other possible causes, such as diabetes mellitus, nutritional deficiencies, chronic renal failure, malignancies, and alcohol abuse.[12]

Frequency

Drug-induced neuropathy does not occur often. Several drugs are associated with neuropathy, for example chemotherapeutics, antibiotics, cardiovascular drugs such as amiodarone, enalapril, hydralazine and the HMG-CoA-reductase inhibitors.[1] The overall prevalence of peripheral neuropathy is approximately 2400 per 100,000 population (2.4%), but in patients older than 55 years the prevalence rises to about 8000 per 100,000.[12] Possible risk factors for developing peripheral neuropathy are hyperlipidaemia,[14] diabetes mellitus and the use of alcohol,[11] with diabetes mellitus being the most important risk factor. The incidence of peripheral neuropathy not associated with alcohol or diabetes is 1.5 per 10,000 person-years.[11,15] The incidence of peripheral neuropathy caused by the use of various drugs is not known. However, epidemiological results suggest that the incidence of peripheral neuropathy associated with the use of HMG-CoA-reductase inhibitors is 1 in 14,000 person-years.[1]

Drug-induced peripheral neuropathy in general occurs shortly after the first exposure to drugs or after a change in medication. However, experiences with HMG-CoA-reductase inhibitors show that neuropathy can also occur many months or years after starting the drug.[13] More important, the risk for neuropathy significantly increases after long-term use of HMG-CoA-reductase inhibitors.

METHODS

The Netherlands Pharmacovigilance Centre Lareb collects and analyses reports of ADRs of marketed drugs provided by health professionals on a voluntary basis on behalf of the Dutch Medicines Evaluation Board. After being received by Lareb, reports are assessed and personalised feedback is provided to the reporter. The reported suspected ADRs are coded using the MedDRA terminology.

The relationship between HMG-CoA-reductase inhibitors and reports concerning neuropathy were evaluated mathematically by computing the reporting odds ratios (ROR). The ROR compares the frequency of the reported ADR for a certain drug with the frequency of reports of that adverse drug reaction for all other drugs in the database. A statistically significant ROR may be indicative of a higher risk for that particular event during the use of a specific medication, but is never conclusive for the actual existence of a causal relation. Additional pharmacoepidemiological studies are needed to determine the actual incidence of a possible ADR. The RORs and 95% confidence intervals (95% CI) were calculated in a case/noncase design.[16] Reports received until 1 June 2005 for which age and gender were reported were included in the analysis. Reports concerning the MedDRA terms neuropathy, peripheral neuropathy and polyneuropathy were considered as cases, all other reports as noncases. Index reports included all reports on an HMG-CoA-reductase inhibitor (ATC code beginning with C10AA); all other reports were controls. The unadjusted ROR and the ROR adjusted for age, gender and the use of antidiabetic medication (ATC code beginning with A10) were calculated by means of logistic regression analysis.[17,18] SPSS software package, version 14, was used for statistical calculations.

RESULTS

Reports in Lareb database

From 1984 to June 2005, Lareb received 17 reports of neuropathy and two reports of aggravation of polyneuropathy associated with the use of HMG-CoA-reductase inhibitors (*table 1*).

Of the 19 reports, nine reports concerned simvastatin, six atorvastatin, three pravastatin and one rosuvastatin. In 13 cases the suspect HMG-CoA-reductase inhibitor was discontinued and in seven of these cases the patient (partially) recovered. The latency period ranges from a few months until years with a mean time to onset of 23.4 months. The time to onset of *de novo* polyneuropathy can be up to 72 months with a mean time to onset of 23.4 months.

Strength of the association

In June 2005 the Lareb database contained 45,325 reports in which the patient's age and gender were known. Of these reports 1911 concerned the use of HMG-CoA-reductase inhibitors and in 18 of them the reported ADR was neuropathy, peripheral neuropathy or polyneuropathy. The characteristics of the HMG-CoA-reductase inhibitors dataset differ significantly from the characteristics of the rest of the dataset (*table 2*). After adjustment for the influence of gender, age and the concomitant use of antidiabetic medication, the ROR for neuropathy – including the MedDRA terms neuropathy, peripheral neuropathy and polyneuropathy and HMG-CoA-reductase inhibitors – was 3.7 (95% CI: 2.2 to 6.2), indicating that neuropathy is significantly more reported during treatment with statins as compared with any other drug class in the Lareb database.

Reports in WHO database

Reports of various pharmacovigilance centres worldwide are forwarded to the database of the World Health Organisation

Table 1. *Reports of neuropathy associated with the use of HMG-CoA-reductase inhibitors*

A	Sex, age	Drug, dose if known	Concomitant medication	Suspected ADR	Time to onset, outcome	Remarks
B	M, 25	Simvastatin, 1 dd 10 mg	Not reported	Neuropathy, paraesthesia of arms and legs	8 months, recovered after withdrawal	
C	F, 59	Simvastatin, 1 dd 20 mg	Enalapril Labetalol	Myopathy, peripheral neuropathy	2 years, not recovered after withdrawal	
D	M, 56	Atorvastatin, 1 dd 20 mg	ASA	Peripheral neuropathy up to knees and hands	5 months, almost completely recovered after withdrawal	
E	M, 65	Pravastatin, 1 dd 10 mg	Lansoprazole Oxazepam ASA	Peripheral neuropathy	2 years, recovered after withdrawal	EMG: no indication for polyneuropathy
F	F, 69	Simvastatin, 1 dd 20 mg	Not reported	Neuropathy (cause unknown)	3 weeks, unknown	
G	M, 71	Pravastatin, 1 dd 40 mg	Lisinopril Budesonide ASA	Pain and burning lower right leg and foot (at night)	5 years, recovering after withdrawal	EMG: no abnormalities, possibly minor neuropathy peroneal nerve
H	M, 77	Simvastatin, 1 dd 40 mg; Sulphamethoxazole/ trimethoprim 2 dd 960 mg	Tamsulosin Omeprazole Amiodarone Amlodipine Furosemide Acenocoumarol Spironolactone Quinapril Prednisolone Triamterene Hydrochlorothiazide	Axonal polyneuropathy, hepatitis, myositis, renal failure	1 year, unknown	EMG: senso-motoric axonal polyneuropathy; patient suffers from progressive renal failure
I	M, 52	Simvastatin, 1 dd 10 mg	Phenytoin	Anoxal polyneuropathy	4 years, unknown	Patient suffers from epilepsy
J	M, 60	Atorvastatin	Dipyramidole Folic acid, enalapril Hydrochlorothiazide ASA	Peripheral neuropathy, cramps in extremities, muscle weakness of legs	6 years, not recovered yet one month after withdrawal	Patient suffers from vitamin B12 deficiency
K	M, 64	Pravastatin, 1 dd 40 mg	Amlodipine, losartan Sotalol ASA	Polyneuropathy	3 weeks, not recovered	
L	V, 63	Atorvastatin, 1 dd 10 mg	Allopurinol Diazepam Furosemide Metoprolol	Peripheral neuropathy, speech and walking difficulties	22 months, five months after withdrawal not yet recovered	EMG: no abnormalities
M	M, 75	Simvastatin, 1 dd 40 mg	ASA Acenocoumarol	Aggravation of existing polyneuropathy	1 day after starting, symptoms decreased after withdrawal	
N	M, 45	Rosuvastatin	Not reported	Polyneuropathy	2 weeks	
O	M, 66	Atorvastatin	Thyroxin Trichlormethiazide Metoprolol ASA	Polyneuropathy	4 years, recovered 1 month after withdrawal	
P	M, 74	Simvastatin	ASA	Aggravation of existing polyneuropathy, erectile dysfunction and decreased ejaculation	12 weeks after starting, not recovered after withdrawal	Medical history of non-progressive polyneuropathy
Q	F, ?	Atorvastatin	Not reported	Polyneuropathy, increased cholesterol levels	Time to onset and outcome unknown	Patient suffers from diabetes mellitus
R	M, 71	Atorvastatin	ASA Diltiazem Enalapril	Polyneuropathy	5.5 years, recovered after withdrawal	
S	M, 45	Simvastatin	Enalapril Hydrochlorothiazide ASA	Polyneuropathy	2 months, simvastatin withdrawn, patient not recovered yet	
T	M, 78	Simvastatin	ASA Metoprolol	Peripheral neuropathy	4.5 years, simvastatin withdrawn patient not recovered yet	Patient suffers from diabetes mellitus

M = male; f = female; ADR = adverse drug reaction; ASA = acetylsalicylic acid; EMG = electromyogram.

Table 2. *Comparison of characteristics of the dataset*

Characteristic	HMG-CoA-reductase inhibitor	Other drugs in the database
Mean age (years)	59.7	53.4
Gender (%)		
• Male	52.4	36.5
• Female	47.6	63.5
Use of concomitant antidiabetic medication (%)		
• Yes	10.0	5.3
• No	89.7	94.7

Table 3. *Reporting odds ratio (ROR) for HMG-CoA-reductase inhibitors in World Health Organisation database*

ADR associated with HMG-CoA-reductase inhibitors	Number of reports	ROR (95% CI)
Neuropathy	245	1.53 (1.34-1.73)
Peripheral neuropathy	469	5.05 (4.59-5.56)
Polyneuropathy	17	4.85 (2.94-8.01)
Total	*731*	*2.86 (2.66-3.09)*

Collaborating Centre for International Drug Monitoring in Uppsala, Sweden[#]. This database contains 733 ADRs of neuropathy, peripheral neuropathy or polyneuropathy, which are disproportionately associated with the use of HMG-CoA-reductase inhibitors. The unadjusted ROR of all HMG-CoA-inhibitors and the combined ADRs was 2.86 (95% CI: 2.66 to 3.09). *Table 3* provides an overview of the reports of the different associations.

DISCUSSION

The Netherlands Pharmacovigilance Centre Lareb received 17 reports of neuropathy and two reports of aggravation of polyneuropathy associated with the use of HMG-CoA-reductase inhibitors.

When considering the plausibility of a causal relationship between the reported neuropathy and the use of HMG-CoA-reductase inhibitors several aspects of the reports play a role, for example the time relationship (latency period, dechallenge or rechallenge), the presence of additional factors (underlying indication of the drug, medical history of the patient), the use of concomitant medication and diagnostic confirmation of the symptoms.

Because the cases in the Lareb database are reported on a voluntary basis they sometimes lack information about the above-mentioned characteristics. Several cases lack information about diagnostic confirmation of the reported symptoms, some patients suffer from diseases that might have contributed to the symptoms: renal failure (H), vitamin B12 deficiency (J), diabetes mellitus (Q and T), and finally the indication (hyperlipidaemia) itself might have induced neuropathy.[14] However, other characteristics of the reports, such as the disappearance of or improvement in the symptoms in seven cases and the relatively long latency period of the reports, support a causal relationship between the symptoms and the use of the HMG-CoA-reductase inhibitors. The long mean time to onset of the neurological symptoms described in reports in the Lareb database is in line with several other studies, supporting the suggestion that especially long-term exposure to HMG-CoA-reductase inhibitors increases the risk of neuropathy. The disappearance of the symptoms after discontinuation of HMG-CoA-reductase inhibitors in eight cases supports a relationship with the use of these drugs.

The exact mechanism by which HMG-CoA-reductase inhibitors can cause neuropathy is still unknown. Since neuropathy has been associated with the use of all HMG-CoA-reductase inhibitors, it appears to be a group effect. Several hypothetical theories about the possible mechanism have been postulated. Firstly, cholesterol is an important component of human cell membranes and therefore HMG-CoA-reductase inhibitors may, by inhibition of the cholesterol synthesis, change the function of nerve membranes.[6] Furthermore it has been suggested that in addition to the cholesterol-lowering effect, a decrease in the level of ubiquinone (coenzyme-Q) may also occur. Ubiquinone is involved in the mitochondrial respiratory chain, which in turn is responsible for the energy production of neurons and striated muscle.[6,11] Both theories could explain structural and functional alterations of the neurons associated with long-term exposure to HMG-CoA-reductase inhibitors.[6]

CONCLUSION

HMG-CoA-reductase inhibitors are used for primary and secondary prevention atherosclerosis. Treatment with HMG-CoA-reductase inhibitors significantly reduces the risk of cardiovascular morbidity and mortality. Polyneuropathy is a very rare side effect of HMG-CoA-reductase inhibitors. Long-term treatment with these drugs increases the risk of polyneuropathy. Considering the increasing number of patients using HMG-CoA-reductase inhibitors and the irreversibility of polyneuropathy, health care professionals should be aware of a possible role of HMG-CoA-reductase inhibitors in neuropathy. Additional research, including electromyography, may be useful.

[#]The views expressed are purely those of the writer and may not in any circumstances be regarded as stating an official position of WHO.

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CASE REPORT

A therapy resistant vasculitis?

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KEYWORDS

EBV, non-Hodgkin's lymphoma, vasculitis

INTRODUCTION

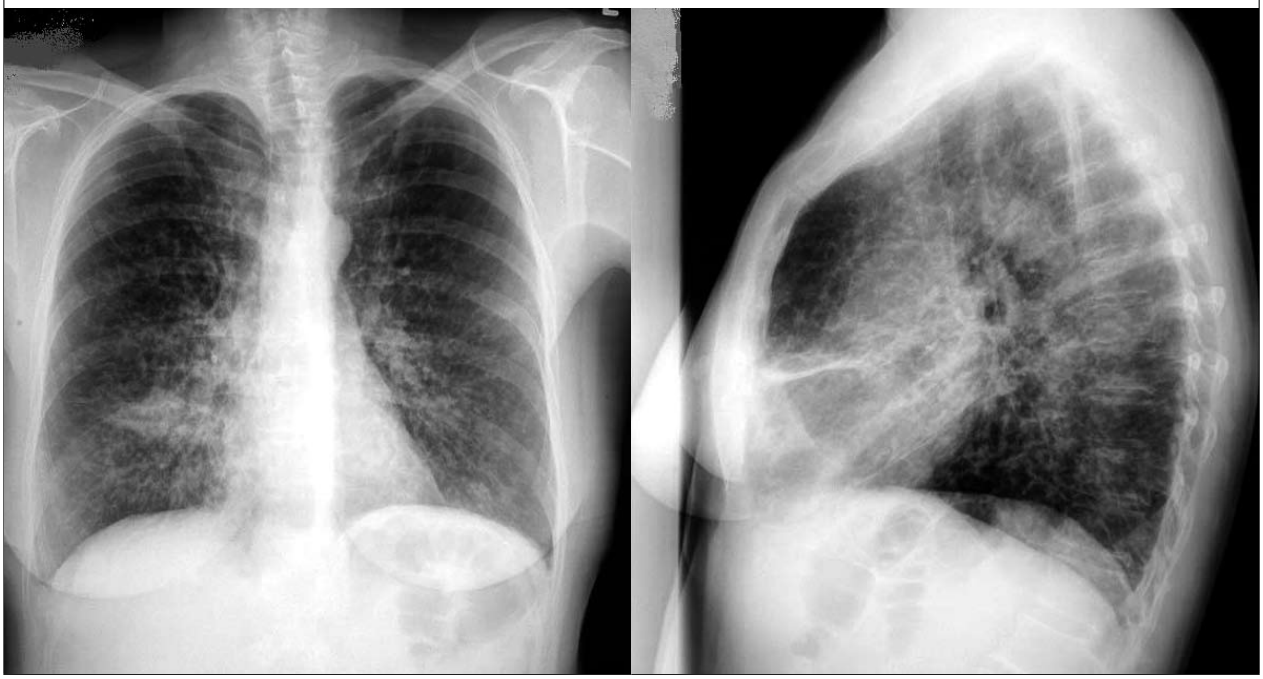
A variety of rheumatic and other autoimmune diseases are treated with immunosuppressive therapy.[1] The therapy often has to be continued for a prolonged period of time, thereby increasing the chance of complications developing and influencing the prognosis of the patient.[1]
Common complications include various forms of organ damage, such as liver failure and bone marrow suppression. In addition, severe (opportunistic) infections and malignancies can occur.[2,3] These complications are frequently accompanied by diagnostic and therapeutic dilemmas mainly due to the atypical course of the disease. In this case, the first occurrence of an Ebstein-Barr virus (EBV)-positive non-Hodgkin's lymphoma during the treatment of Wegener's disease with azathioprine is described.[1-3] Partly because of this extremely rare combination, the diagnostic and therapeutic procedures were complicated.

CASE REPORT

A 60-year-old woman presented to the Emergency Unit because of severe dyspnoea and fever. In the previous two months she complained of progressive cough with production of white sputum, and progressive fatigue. Wegener's disease had been diagnosed in this patient 2½ years earlier, based on c-ANCA and anti-PR3 positive arthritis, pneumonitis and glomerulonephritis, which was in full remission under treatment with prednisone and azathioprine. She had initially been treated with cyclophosphamide, followed by azathioprine and prednisone. The azathioprine had been discontinued one month earlier because of leucopenia and thrombocytopenia.

Physical examination revealed a non-dyspnoeic woman with a body temperature of 39.0°C. She had herpes labialis. Auscultation revealed crackles over both lungs. Liver, spleen and lymph nodes were not palpable.
Laboratory investigation showed a haemoglobin (Hb) of 7.1 mmol/l (7.5-10.0), white blood cell count 4.3 x 10^9/l (4.0-11.0), thrombocyte count 122 x 10^9/l (150-400), erythrocyte sedimentation rate 44 mm/h (<20), C-reactive protein (CRP) 186 mg/l (0-10), sodium 128 mmol/l (135-145), creatinine 97 μmol/l (70-100), slightly elevated γ-glutamyltranspeptidase and transaminase, and a lactate dehydrogenase of 614 U/l (135-225). c-ANCA-IF and anti-PR3 remained negative. Urine analysis revealed no protein or cylinders. The arterial blood gas analysis showed the presence of a respiratory alkalosis with hypoxia.
The chest X-ray showed bilateral diffuse reticulo-nodular abnormalities with a consolidation in the right middle lobe (*figure 1*).
Microbiological investigations remained negative. Cultures of blood and bronchoscopic fluid were negative for *Pneumocystis carinii* pneumonia, cytomegalovirus, tuberculosis, EBV, respiratory viruses, mycoplasma, *Chlamydia* and other micro-organisms. Virus serology did not provide evidence of the presence of an acute viral infection. In addition, the *Legionella* test remained negative. Bronchoscopy revealed the presence of bronchitis.
Under the suspicion of a bacterial infection during immunosuppressive therapy the patient was initially treated with a high dose of cotrimoxazole, pending further investigation. In addition she was treated with valaciclovir because of the suspicion of infection by the herpes virus. Initially these therapeutic measures led to a short clinical improvement with normalisation of her body temperature and CRP. Shortly thereafter, however, her condition deteriorated with complaints of dyspnoea, hypoxia and fever. In the differential diagnosis reactivation of Wegener's disease was considered. In addition, the presence of an opportunistic infection, a second autoimmune disease or

Figure 1. *Chest X-ray of patient on admission*



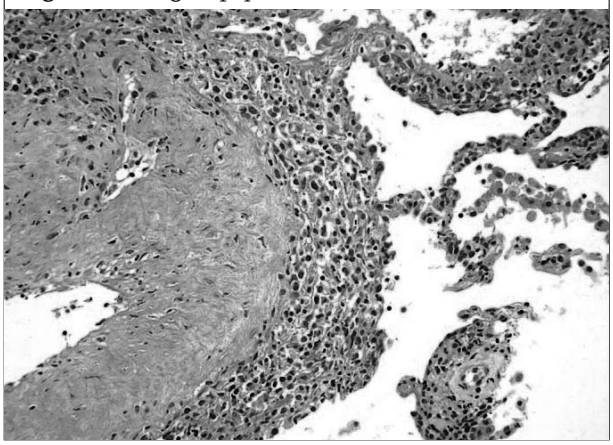
malignancy were all included in the differential diagnosis. Pathological investigation of the transbronchial biopsies showed vasculitis of the smaller to middle-size vessels, without fibrinoid necrosis (*figure 2*). Because cultures and the first serological investigation remained negative, therapy was started with prednisone pulse therapy.

The clinical situation became complicated by melaena, haemodynamic instability and progressive respiratory failure. Gastroscopy revealed an erosive oesophago-gastroduodenitis, which was treated with proton pump inhibition. Because still no clinical improvement was seen after initiation of the prednisone pulse therapy, cyclophosphamide was added, after a bone marrow sample taken from the sternum showed no abnormalities.

On day 18 after admission the patient was admitted to the ICU because of progressive respiratory insufficiency and exhaustion. She was sedated, intubated and mechanically ventilated. At that time she had developed leucopenia, thrombopenia as well as anaemia with a decreasing Hb concentration to 3.0 mmol/l, which was treated with a blood transfusion. In spite of maximal support of the vital functions, the patient died as a consequence of multi-organ failure.

Postmortem investigation revealed diffuse petechiae and haematomas in the skin of the torso and extremities. There was a bilateral pneumonia and bilateral pleural effusions. In addition haemorrhagic lesions based on vasculitis of the small and middle-size arteries were found to be diffuse in the lungs, kidneys, adrenal glands and liver. The liver and spleen were enlarged. A perforation was found in the distal part of the ileum, 6 cm in front of the valvula bauhini. More distal blood clots and blood were seen in the colon and rectum.

Figure 2. *Lung biopsy 10 x HEion*



Cultures taken during autopsy from the lungs and spleen revealed growth of *Staphylococcus aureus*. In several different organs, in particular in the adrenal glands, cytomegalovirus was found. Additional investigation showed groups of atypical cells in various organs. Atypical cell proliferation of lymphoid and plasmacytoid cells was particularly seen around the perforation of the distal ileum, immunohistochemically matching an EBV-positive B-cell non-Hodgkin's lymphoma.

DISCUSSION

Development of EBV-related lymphoproliferative diseases is regularly reported in patients on immunosuppressive therapy after an organ transplant or during treatment

with methotrexate (MTX) because of rheumatic disease.[1-3] Generally it involves B-cell lymphomas but occasionally T-cell lymphomas, which in some instances are detected as early as after six months of therapy. Occasionally the lymphomas show remission after suspension of the immunosuppressive therapy.[4,5] The majority of the documented cases are EBV-related lymphomas during treatment with MTX. We have not been able to find any documentation on lymphomas developing during treatment with azathioprine because of Wegener's disease. The fact that the bone marrow specimen and the haematological parameters normalised after suspension of the azathioprine suggested that the azathioprine had caused the leucopenia and thrombopenia, which had developed in the month prior to admission. At first, on the basis of the clinical presentation in combination with the finding on the chest X-ray, we assumed the presence of an opportunistic infection. Only after microbiological investigation remained negative and supported by the results of transbronchial lung biopsies, therapy with immunosuppressive therapy was initiated. Since there was no clinical improvement, other diagnostic options were considered. Although c-ANCA and anti-PR3 were negative in this previously positive case of Wegener vasculitis recurrence remains a possible diagnosis. One study reported six ANCA-negative relapses out of 13 patients.[6] In another report a patient with vasculitis was presented with recurrent nodules on the chest X-ray without recurrence of anti-PR3 antibodies.[7] Retrospectively perivascular infiltrates with EBV-positive lymphoma cells were found in the transbronchial lung biopsies after additional immunohistochemical testing. A prompt diagnosis of non-Hodgkin's lymphoma could possibly have led to other therapeutic strategies such as treatment with rituximab.[8,9] This case presents an extremely rare combination of diseases, which has not been described previously.

CONCLUSION

Although a relapse of vasculitis is a possibility in the case of a PR3-negative reticulonodular pulmonary infiltrates in a previously c-ANCA and PR3 positive Wegener vasculitis, the differential diagnosis should be extended to a specific search for EBV and associated lymphoreticular malignancy.

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CASE REPORT

Sarcoidosis mimicking metastatic disease: a case report and review of the literature

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ABSTRACT

Osseous and in particular vertebral sarcoidosis is exceedingly rare and a difficult diagnosis to establish because it may simulate many diseases, including even metastatic malignancy. We present a patient with lesions in bones, lungs and lymph nodes, mimicking the presence of extensive metastatic disease. Our case emphasises the importance of histological evidence before the diagnosis of osseous sarcoidosis can be made with confidence.

KEYWORDS

Besnier-Boeck-Schaumann, hypercalcaemia, vertebral, sarcoidosis

INTRODUCTION

Sarcoidosis is a chronic granulomatous multisystem disease of unknown aetiology, which usually affects young adults. The diagnosis of sarcoidosis is made by a combination of clinical, radiological and histological findings. Symptoms are weight loss, fatigue, fever, night sweats, coughing and shortness of breath. On the X-ray of the chest a spectrum of abnormalities can be seen varying from lymphadenopathy to extensive parenchymal destruction.

However, histological proof with noncaseating granulomata remains the hallmark of this disease. The diagnosis is sometimes difficult to establish, because sarcoidosis may simulate many diseases, including even metastatic malignancies. We present a patient with lesions in bones, lungs and lymph nodes, mimicking the presence of extensive metastatic disease.

CASE REPORT

A 61-year-old asymptomatic white male, working as a carpenter, was referred to our hospital with renal function impairment, with a creatinine of 123 μmol/ (70-110 μmol/) which was found on a routine check-up in June 2004. Physical examination showed no abnormalities. Routine laboratory tests showed a creatinine of 111 μmol/l, creatinine clearance 91 ml/min, a calcium of 3.15 mmol/l (2.20-2.60 mmol/l), with a normal albumin value of 41 g/l (34-48 g/l), serum phosphate concentration of 0.94 mmol/l (0.75-1.45 mmol/l) and an erythrocyte sedimentation rate of 37 mm/h (0-20 mm/h). Further laboratory tests showed a parathormone <0.4 pmol/l (0.6-4.2 pmol/l), 25-hydroxy vitamin D concentration of 68 nmol/l (25-160 nmol/l), thyroid-stimuating hormone of 1.5 mU/l (0.3-4.0 mU/l), normal angiotensin-converting enzyme level of 48 U/l (12-68 U/l) and normal serum protein electrophoresis. A chest X-ray revealed multiple pulmonary nodules in the right lower lobe and broadening of the mediastinum, suspicious for pulmonary metastases and extensive mediastinal lymphadenopathy (*figure 1*). A Tc-99m HDP whole-body bone scan revealed numerous hot spots, mainly axial, which was highly suggestive of extensive metastatic disease (*figure 2*). Total spine magnetic resonance imaging (MRI) showed abnormal marrow signal intensity within several vertebral bodies (*figure 3 A-B*), without radiological signs of cord compression. Extensive bone lesions were also observed in both iliac bones (*figure 3 C-D*), acetabulum and proximal femurs. All of these findings were highly suggestive of metastatic disease. Further work-up included a computed tomography (CT) scan of the chest and abdomen, which showed multiple lung lesions and enlarged mediastinal lymph nodes, suggesting extensive lung and lymph node metastases (*figure 4*). In the abdomen enlarged lymph nodes were mainly found along the aorta and the iliac artery. A lesion in the spleen was observed, suggesting spleen metastasis. Bone biopsy of the iliac

Figure 1. *Chest radiograph revealing reticulonodular interstitial disease in the lower lobes, hilar lymphadenopathy and broadening of the mediastinum*

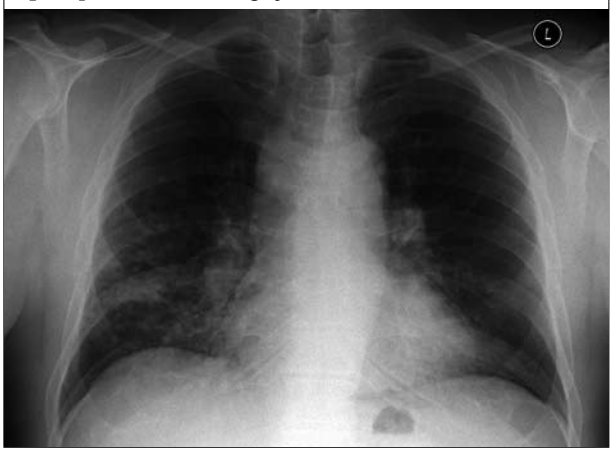


Figure 2. *Tc-99m HDP bone scintigraphy showing multiple focal areas of abnormal radiotracer accumulation mainly in the axial skeleton, but also in the left shoulder region, both iliac bones, hips and left ankle*

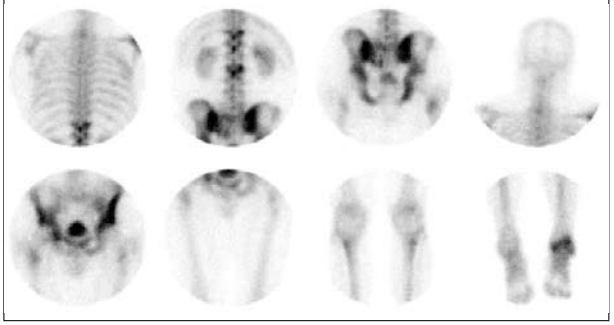
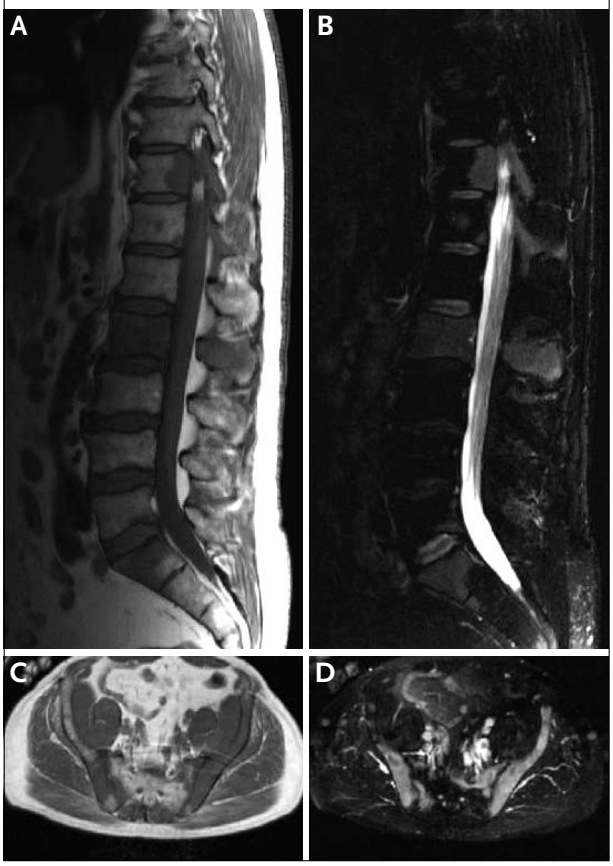
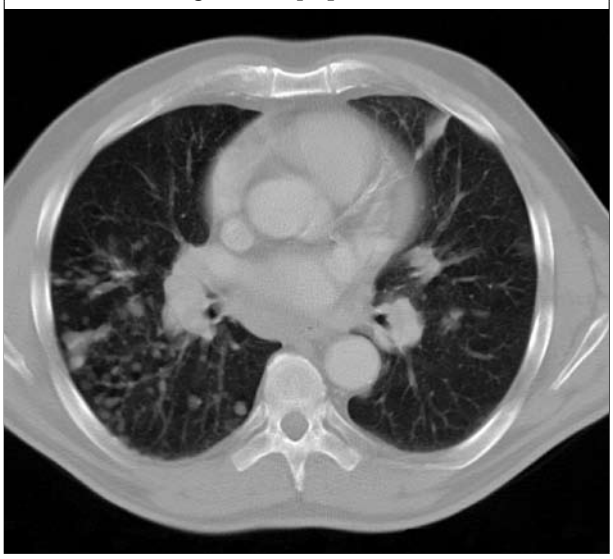


Figure 3. *A) Sagittal T1-weighted MRI showing multiple low signal lesions in the vertebral bodies and enlarged abdominal lymph nodes, B) T2-weighted sequences showing hyperintensive vertebral lesions, C) Axial T1-weighted MRI demonstrating hypointense lesions in both iliac bones and D) The iliac lesions have a high signal intensity in T2-weighted sequences*



bone demonstrated the presence of epithelioid granulomas and giant cells (*figure 5*). The same was found in biopsy specimens of peripheral lung tissue. Polymerase chain reaction on mycobacteria was negative. These pathological findings were consistent with sarcoidosis and because of the hypercalcaemia, treatment followed with prednisolone 20 mg/day. After six months of treatment the patient is still asymptomatic while calcium and renal function have normalised. A second MRI of the spine showed an amelioration in signal intensity without, however, a decrease in the number and volume of the lesions.

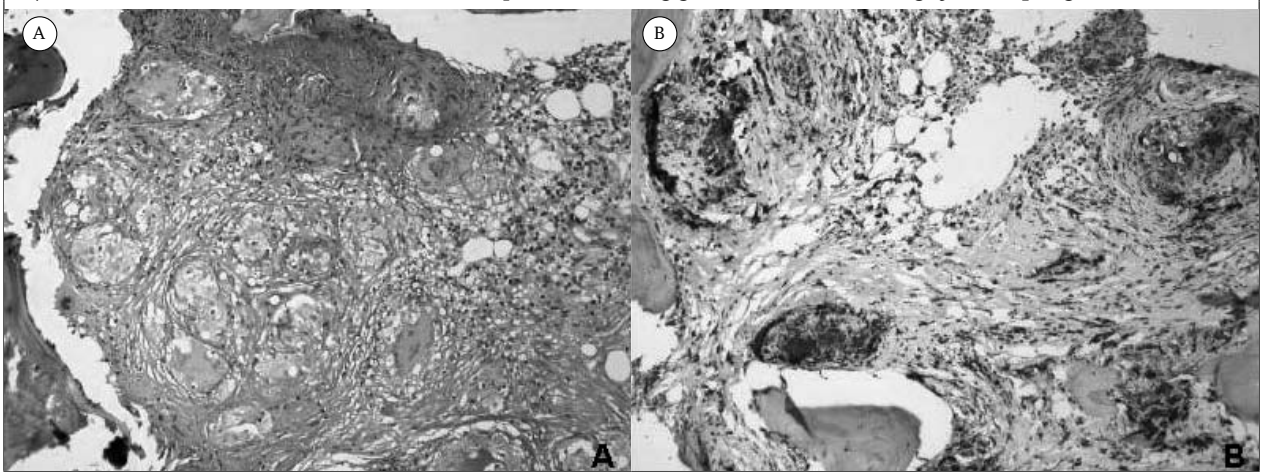
Figure 4. *CT scan of the chest showing multiple lung lesions and enlarged hilar lymph nodes*



DISCUSSION

Sarcoidosis is a multisystem disorder characterised by noncaseating granulomatous infiltration. The most common sites of involvement are lungs and lymph nodes, while other organs such as spleen, liver, skin, eyes, muscles, bones, central nervous system and salivary

Figure 5. *A) Bone marrow biopsy from the iliac bone stained with periodic acid-Schiff (PAS), showing multiple epithelioid granulomata and giant cells*
B) section stained with an anti-CD68 antibody demonstrating granulomata consisting of macrophages



glands are less frequently involved.[1] With this variety of organs involved, sarcoidosis can mimic other diseases. In our case, the patient was thought to have disseminated metastatic malignancy, based on bone scintigraphy, MRI and chest plus abdominal CT suggesting bone, lung, lymph node and spleen metastasis. In 2003 Haluska *et al.* presented a similar patient who was presumed to have widespread metastatic melanoma; vertebral MRI lesions suggested metastatic neoplasm. However, these lesions turned out to be nonnecrotising granulomas consistent with sarcoidosis.[2] Ludwig *et al.* reported a patient presenting with low back pain, who was also thought to have metastatic skeletal disease based on MRI, bone scintigraphy chest CT and FDG-PET imaging, which also turned out to be sarcoidosis.[3] A similar case was also reported by Mangino *et al.*[4]

Osseous involvement is relatively uncommon in sarcoidosis. The incidence varies from 1 to 13%.[5] Most cases of osseous sarcoidosis occur in the long bones of the hands and feet.[6] Vertebral involvement in sarcoidosis is exceedingly rare with less than 30 cases reported.[4] A consistent feature of previous reports of vertebral sarcoidosis is back pain,[7,8] but our case shows that extensive vertebral bone lesions can be present without symptoms, with hypercalcaemia as sole abnormality. Granulomas in sarcoidosis provide a nonrenal source of 1,25-dihydroxy-vitamin D3, which has been demonstrated in lymph nodes and in alveolar macrophages. This hyperproduction may result in enhanced intestinal calcium absorption leading to hypercalcaemia.[9] In our case, however, the vitamin D concentration was normal, so the hypercalcaemia in our patient was most likely due to the observed bone lesions.

Bone scintigraphy has been reported rarely in vertebral sarcoidosis.[2,3,7] Although nonspecific, it may be a sensitive indicator of the extent of osseous sarcoidosis and has potential diagnostic utility in that it can localise sites for biopsy if the clinical area is not readily accessible.[7] In a few cases MRI findings in vertebral sarcoidosis have been reported.[2-5,7,8,10-12] MRI usually demonstrates multifocal lesions within the vertebrae that are hypointense (low-signal intensity) on T_1-weighted images and hyperintense (high-signal intensity) on T_2-weighted images, which enhance following contrast medium administration.[4,10] Multifocal vertebral body lesions have a broad differential diagnosis that typically includes metastatic disease (in particular prostate, breast and lung), lymphoma, myeloma, Paget's disease, osteomyelitis, renal osteodystrophy and granulomatous diseases, which stresses the need for further investigation. The rarity of osseous and in particular vertebral sarcoidosis plus its nonspecific imaging manifestations often lead to a significant delay in diagnosis.[8]

Management of bone sarcoidosis remains controversial, and randomised controlled trials have not been reported. Indications for therapy are not well defined, but pain, bone destruction and hypercalcaemia usually require treatment.[13] In our case, hypercalcaemia was the indication for therapy. Calcium can exert toxic effects on renal tubules and may lead to nephrogenic diabetes insipidus and by interstitial calcium deposition to nephrocalcinosis and chronic renal insufficiency.[9] Corticosteroids are the therapy of choice and long-term efficacy in osseous sarcoidosis has been suggested.[14] Moreover, prednisolone in relatively low doses (10-20 mg/day) is effective in rapidly correcting hypercalcaemia in sarcoidosis.[9] Symptoms are usually controlled, but radiographs may not show improvement.[15] In our case, the calcium normalised by treatment with prednisolone 20 mg/day. After 11 months a second MRI of the spine showed an amelioration in signal intensity, without, however, a decrease in the number and volume of the lesions. Rua-Figueroa *et al.* reported a change to normal signal on vertebral MRI long after a clinical response to treatment.[7]

In conclusion, osseous and in particular vertebral sarcoidosis is exceedingly rare and a difficult diagnosis to establish because of the resemblance to other diseases, including even metastatic malignancy. This case emphasises the importance of histological evidence, before the diagnosis of osseous sarcoidosis can be made with confidence.

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CASE REPORT

Sclerosing peritonitis: an unusual cause of ascites in a patient with systemic lupus erythematosus

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ABSTRACT

Sclerosing peritonitis is a rare condition characterised by fibrosis and adhesion of the peritoneum to loops of the small intestine. It is generally associated with continuous peritoneal dialysis, peritoneo-venous shunts or β-adrenergic blocking agents. In this case we report a female patient with idiopathic sclerosing peritonitis and systemic lupus erythematosus.

KEYWORDS

Fibrosis, idiopathic, paraneoplastic, sclerosing peritonitis

CASE REPORT

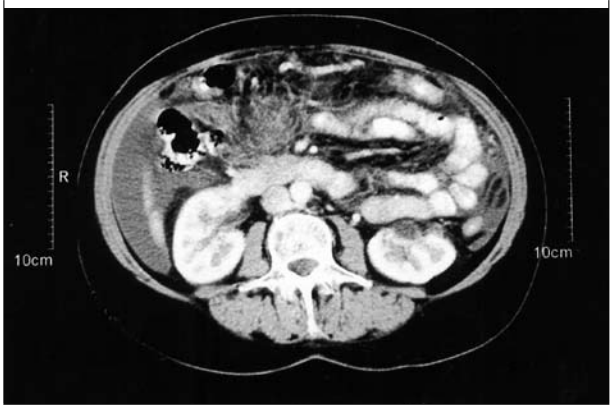
A 62-year-old female patient was admitted to our hospital because of progressive abdominal distension, anorexia and a weight gain of 3 kg in two months. At the moment of presentation she was only taking codeine because of a cough.

Her medical history showed two spontaneous abortions, alopecia areata, and 18 months ago she developed thrombocytopenia (thrombocytes <1 x 10^9/l) with an IgM monoclonal peak of 1.8 g/l. A bone marrow examination at that moment revealed a normal number of megakaryocytes, plasma cells and no evidence of lymphoma. In a 24-hour urine collection no Bence Jones or other proteins were detectable. Since no systemic symptoms were present, autoimmune thrombocytopenic purpura was diagnosed and initially treated with prednisone, which resulted in a recovery of the thrombocytes to normal in seven days. The prednisone was decreased and stopped after two months. Subsequent blood controls were all normal. Her family history was negative. Clinical examination during admission showed a substantial abdominal distension induced by ascites. Rectal and vaginal examination were normal.

Laboratory examinations including haematology were normal (thrombocytes 280 x 10^9/l), biochemistry showed a total protein of 65 g/l (normal: 63-82 g/l), an albumin of 30 g/l (normal: 35-50 g/l). CA-125 was 176 U/ml (normal <35 U/ml), α-fetoprotein was 12 kU/l (normal <5.8). Thyroid stimulating hormone, anti-DNA antibodies, lupus anticoagulants, anticardiolipine antibodies, ENA, p-ANCA, c-ANCA and MPO were all normal. Chest X-ray showed a little infiltration in the middle lobe and a small pleural effusion on the right. This resolved in subsequent controls. Computed tomography (CT) of the abdomen showed a liver cyst, massive ascites, normal internal organs and normal omentum. The fluid of abdominal paracentesis was clear containing limited WBC/mm^3, protein 50.1 g/l and lactate dehydrogenase (LDH) 136 IU/l. Cytological studies were negative for malignant cells, and only showed reactive mesothelium cells. Cultures were negative for bacteria, fungi and tubercle bacilli. A gynaecological echoscopic examination showed atrophic ovaria, but no signs of carcinoma. For the slight lung infiltrate, a bronchoscopy with a broncho-alveolar lavage was carried out, which appeared to be normal for microbiology and pathology. With the suspicion of an autoimmune disorder (not fulfilling the minimal criteria of systemic lupus erythematosus (SLE)) she was treated with prednisone 60 mg/day for six weeks, without a recurrence of the ascites. However, six weeks after stopping the corticosteroids there was a relapse in the ascites and at that moment an abdominal CT scan showed a peritoneal thickening (*figure 1*).

A diagnostic abdominal laparotomy, by a surgical oncologist, revealed an image resembling a peritonitis carcinomatosis with a very stiff omentum. Five litres of ascites were removed

Figure 1. *Abdominal CT scan showing the thickened peritoneal mesothelium*



and multiple biopsies from peritoneum and omentum were taken. Slides of the pathological examination of the thickened peritoneum showed a chronic fibrosing inflammation with a lot of histiocytic multinucleated giant cells, surrounding an arborising proliferation of capillary vessels and fibromyoblasts. The giant cells showed a strong expression of Vimentine, S100, ACT and a low expression of AAT and CD68. There was no expression of AEl/AE3, CEA or EMA in these areas. No carcinomatous or sarcomatous proliferation was present and no foreign body material was seen.

Three months after surgery she presented with a relapse in the ascites and prednisone 60 mg/day was started. The prednisone was gradually decreased to 15 mg/day and azathioprine 100 mg/day was added, which resulted in the ascites resolving. She had been treated with both medicines for six months, but at that moment they had been discontinued because she developed dyspnoea and fever with a suspected immunocompromised infection.

A chest X-ray showed infiltration of the left basal lobe and a small pleural effusion. She was treated with sulphamethoxazole/trimethoprim and doxycyline. A bronchoscopy and broncheo-alveolar lavage was carried out but no micro-organism was identified. After a short improvement, the dyspnoea showed acute progression.

CT angiography of the thorax showed pulmonary embolism. Our patient was treated with acenocoumarol. Echo duplex of the leg veins showed no venous thrombosis. An abdominal ultrasound showed no ascites and normal internal organs. The cause of the pulmonary embolism was unknown at that moment. There was no evidence of malignancy, and examinations for disorders of coagulation were planned after anticoagulation had been stopped. Because of anaemia (Hb 6.1 mmol/l) and arthralgia a laboratory examination was performed, which showed an abnormal titre of anti-ds DNA antibody of 20.5 kU/l (normal <10). ANCA and MPO antibodies were negative.

Ten months later she presented with severe anaemia, dyspnoea and tiredness. Her medication consisted of acenocoumarol. Clinical examination showed basal decreased pulmonary sounds and evidence of ascites. Laboratory examinations showed a haemoglobin of 3.5 mmol/l (normal 7.5-9.9), LDH of 735 U/l (normal <480), bilirubin of 29 µmol/l (normal 3-22) and reticulocytes of 187 ‰ (normal 4-42). Direct and indirect Coombs tests were positive. Her serum showed cold and warm autoagglutinins. Leucocytes and thrombocytes were normal. CT of the thorax and abdomen showed slight pleural effusion and ascites, with normal internal organs. Further tests were performed to exclude an autoimmune disease. ANF was 800 U/ml (normal <50), anti-ds DNA was 4.5 kU/L (normal <10), lupus anticoagulant was positive. MPO and proteinase 3 antibodies were negative. Because she currently had serositis (pleuritis and ascites), haemolytic anaemia and lupus anticoagulant, and the antinuclear antibody titre had been abnormal one year previously, the diagnosis of systemic lupus erythematosus was made in our patient.

Treatment of the autoimmune haemolytic anaemia and SLE consisted of prednisone 100 mg/day which was gradually decreased. The haemoglobin increased from 3.5 to 6.7 mmol/l in four weeks and she had no complaints of dyspnoea or tiredness.

DISCUSSION

Sclerosing peritonitis is a rare disease characterised by fibrosis and adhesion of the peritoneum. It is a myofibroblastic spindle cell proliferation involving the peritoneal surfaces. The peritoneum is thickened, adhesions may be prominent, resulting in an abdominal cocoon. Myofibroblastic spindle cells accompanied by variable amounts of collagen form the fibrous peritoneal membrane.[1] With progression of the fibrosing and sclerosing process, the bowel is ultimately invaded and encased in a 'fibrous cocoon', at which point the term 'sclerosing encapsulating peritonitis' is used.[2,3] This occurs in up to 90% of patients.[3] This situation leads to a significant morbidity due to bowel obstruction and sepsis, with mortality rates up to 80%.[3]

Most reported cases have been secondary to chronic peritoneal dialysis.[2] Fortunately, in this setting it affects less than 1% of the patients.[3] However, some suggest this may be an underestimation of its prevalence due to its insidious nature.[3] In this setting, several factors have been reported to be responsible for this syndrome: the use of acetate buffer or hypertonic glucose, disinfectants such as chlorhexidine and povidine iodide, catheters, in-line bacterial filters, particles of plastics and plasticisers.[4,5]

Patients with peritoneal sclerosis have a higher incidence of infective peritonitis than patients without the condition. A severe episode of peritonitis, particularly pseudomonal or fungal, often precedes the onset of encapsulating peritonitis.[6]

In these cases this disease can be seen as a consequence of an abnormal reaction of the peritoneum to a chronic stimulus. However, peritoneal sclerosis has also been described in nondialysis patients. Best known is the association between the use of β-blockers and sclerosing peritonitis, reported for the first time by Brown in 1974 with the use of practolol. There have also been reports with other β-blockers.[4] Some reports describe this entity secondary to LeVeen peritoneovenous shunts in cirrhotic patients and to ventriculoperitoneal shunts.[2,5-7] Associations with various tumours are also described: with gastric cancer, ovarian thecoma, ovarian teratoma, pancreas carcinoma and renal carcinoma, where the sclerosing peritonitis might be a paraneoplastic phenomenon.[4]

Until now only 17 cases of idiopathic sclerosing peritonitis have been described. Garosi divides this entity into two categories. The first category is associated with other conditions as retroperitoneal fibrosis or pericardial sclerosis which can be a systemic connective tissue impairment. In the second category authors report a genetic predisposition. The early reports on this condition showed a high frequency in young adolescent women in subtropical areas, all with a small bowel obstruction. These were familial forms.[2,4] The authors strongly believe that the genetic predisposition may be the basic trigger for the development of sclerosing peritonitis.[4]

Regarding the cause of the sclerosing peritonitis in our patient, we found no evidence of a paraneoplastic phenomenon after extensive work-up. She had never taken β-blockers and she had no history of infective peritonitis. Odama *et al.* described the co-occurrence of sclerosing peritonitis and SLE in two patients with continuous ambulant peritoneal dialysis. Until now, no reports have been made about nondialysis patients with SLE presenting with sclerosing peritonitis.[3] Our patient presented with recurrent ascites and sclerosing peritonitis. This has not been described before. After a diagnosis of SLE there is usually inflammation of serosal membranes with subsequent peritonitis, pleuritis or pericarditis.[6] Autopsy studies have shown evidence of previous peritoneal inflammation in 63 and 72% of patients with SLE.[7,8] Serositis rarely causes significant ascites.[7] Ascites, a marker of peritoneal irritation, was only detected in 8% of lupus patients in one study and 11% in another,[8,7] which is significantly less than pleural or pericardial effusions. Ascites typically has a gradual onset and occurs after a diagnosis of SLE has been made and it is rarely massive. When patients had massive ascites, SLE was usually diagnosed years earlier; disease activity did not correlate with the course of ascites.[9,10] Some degree of ascites is usually associated with nephrotic syndrome, protein-losing enteropathy, constrictive pericarditis, congestive heart failure, or Budd-Chiari syndrome.[11] Cirrhosis, pancreatitis, peritoneal carcinomatosis and tuberculous peritonitis should also be excluded. Marked ascites has been attributed to chronic lupus peritonitis.[12-17] This is characterised by the insidious onset of massive, painless ascites. When pain is present it is attributed to massive distention.

Our patient presented with three recurrences of ascites, which responded initially to immunosuppressive therapy. At the time of the first recurrence peritoneal biopsies already showed chronic fibrosing inflammation. A chronic serositis as a symptom of SLE may have finally led to the sclerosing peritonitis. What is remarkable is the insidious onset of her symptoms, which resulted in a delay in the diagnosis and therapy. Also, no other apparent symptoms of SLE were present until the second recurrence, and the criteria of SLE were only fulfilled at the third recurrence of ascites.

The presentation is relatively uniform regardless of the cause. The clinical manifestations have an insidious onset with episodes of abdominal pain. Later patients develop nausea, vomiting associated with weight loss and ascites. Sometimes the presentation is acute with a painful abdominal mass, and bowel obstruction.[4,9] Peritoneal dialysis patients also experience ultrafiltration failure.[8] Because the early clinical features are nonspecific, patients are often not recognised until they develop complications. The most common complications appear to be small bowel obstruction, bowel necrosis, and enterocutaneous fistulae, all of which necessitate surgical intervention.[10] Regarding the diagnosis our patient underwent laparoscopic biopsies. There is no reliable noninvasive method for screening for sclerosing peritonitis. Since mesothelial cell injury and loss precede the development of fibrosis, some suggest the routine assessment of markers of mesothelial cell mass in peritoneal effluent, such as CA125. A sudden and persistent decrease in the level of CA125 in the peritoneal effluent has been associated with the presence of sclerosing peritonitis.[3] The provisional diagnosis of sclerosing peritonitis can be made by CT, which provides information about the ascites, calcifications and thickening of the peritoneum.[4,11-18] The diagnosis is confirmed by surgical exploration and histological examination of peritoneal biopsy.[4] The macroscopic aspect of the peritoneum is grossly altered: the surface is reduced to a rough thickened membrane. The microscopic picture is dominated by sclerosis. In many cases there is a cellular infiltrate in the sclerotic tissue, which can contain leucocytes, erythrocytes, macrophages and giant cells.[12-19] Calcifications and severe vascular alterations also occur.[13-19] An increase in mesothelial cell surface area and the emergence of giant cells in the effluent indicate advanced histopathology, and may be useful indicators to prevent the development of sclerosing encapsulating peritonitis.[14-20]

The overall prognosis is poor after a sclerosing encapsulating peritonitis has developed, because it often results in death from complications due to bowel obstruction and sepsis.[3] The reported death rate of encapsulated sclerosing peritonitis is more than 60% within four months of diagnosis.

Surgery is needed in cases of intestinal obstruction.[4] This is often complicated because of severe adhesion of the peritoneum.[15-21] No surgical treatment is required in ascites, asymptomatic sclerosing encapsulating peritonitis or subacute intestinal obstruction.[16-22] In our patient the small bowel was not incised because there was no evidence of small bowel obstruction. In cases associated with peritoneal dialysis removal of the catheter is needed and often results in improvement of the symptoms and regression of the anatomic lesions.

Many case reports describe the singular or combined use of steroids and immunosuppressants. Most of them report success with at least a longer survival. Junor described this for the first time in 1993, his patients treated with prednisone 30 to 50 mg/day, in some cases supplemented with 100 to 125 mg/day azathioprine, outlived the patients not treated with immunosuppressants.[17-23] But these results remain difficult to interpret because the efficacy of the treatment depends of the stage in which the therapy is started.[18-24] Peritoneal sclerosis usually develops with fever, increased levels of C-reactive protein, slight ileus symptoms and ascites. Precise identification of this 'inflammatory stage' should guide initiation of steroid administration.[19-25] Other authors suggest that since some patients have signs of a chronic infection, the use of antibiotic therapy should be examined. This has now been studied in Italy by the Peritoneal Dialysis Study Group.[4]

Tamoxifen has been successfully used in the treatment of retroperitoneal fibrosis. A case-control study of 23 peritoneal dialysis patients with peritoneal sclerosis treated with tamoxifen 40 mg/day for a mean of 14 months resulted in prevention of encapsulating peritoneal sclerosis and a significantly lower mortality (22 *vs* 71%) in the treated patients.[19-26] In another study subsequent CT of a patient treated with tamoxifen showed significant reduction in the thickness of the peritoneum, perhaps induced by angiogenesis inhibition.[20-27]

No earlier reports have been made about a patient with SLE who initially presented with a sclerosing peritonitis. The high mortality rate of sclerosing encapsulating peritonitis has emphasised the need to develop preventive strategies. It is clear that this rare and serious disease needs further research regarding the aetiology and possible therapies. When this entity is diagnosed primary mechanisms must be excluded.

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PHOTO QUIZ

The ECG in hypothermia: Osborn waves

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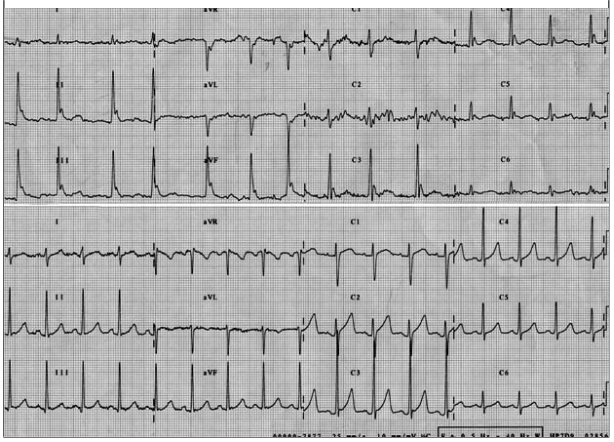
CASE REPORT

A 26-year-old man was referred to our Emergency Room with mental confusion and accidental hypothermia. After attempting to run away, partly through water, he was found more than one hour later in a field. He was in a comatose, hypothermic state and unresponsive. The Glasgow Coma Scale was 2-4-1, with an irregular pulse of 120 beats/min and a blood pressure of 130/85 mmHg. Rectal temperature measured 27.9°C. Physical examination revealed small but normally reactive pupils, extremities were cold without reflexes. He was shaking heavily. Laboratory investigation was normal.

WHAT IS YOUR DIAGNOSIS?

See page 353 for the answer to this photo quiz.

Figure 1. *ECG during hypothermia (29°C)*



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Tension pneumothorax with a patent thoracostomy tube

Dear Sir,
A pneumothorax is usually easy to treat. However, even with a patent thoracostomy tube, the problem might not be resolved as the following case shows.

CASE REPORT

A 64-year-old previously healthy male was admitted to the emergency department with sudden acute dyspnoea. No trauma had occurred. He had a history of heavy smoking for over 20 years. On presentation to the emergency room the patient was deeply cyanotic, dyspnoeic and extremely agitated. There was no clubbing or peripheral cyanosis. The vital signs were as follows: blood pressure 90/52 mmHg, pulse 112 beats/min, respiratory rate 36 breaths/min and temperature 38.2°C. Oxygen saturation was 76% on room air. On auscultation severe wheezing and decreased breath sounds were heard on the right side. Cardiac examination was normal.

Chest X-ray showed a large right-sided pneumothorax (figure 1). Lateral thoracostomy was immediately performed and control chest X-ray showed an adequate positioning and resolution of the pneumothorax (figure 2). After further clinical improvement the patient suddenly developed renewed respiratory distress and hypotension. Under the clinical suspicion of recurrent pneumothorax, despite a thoracostomy tube already in place, a new chest X-ray was performed and our suspicion was confirmed (figure 3).
Computed tomography (CT) scan of the chest, after insertion of a second thoracostomy tube ventrally, showed giant emphysematous bullae of the lungs with a remaining right-sided anterior pneumothorax (figure 4).
The patient had to be intubated and mechanically ventilated due to progressive respiratory failure.
The thoracic surgeons were consulted because of massive air leakage through both tubes. Video-assisted thoracic surgery (VATS) with bullectomy and pleurodesis was performed.
Postoperatively the patient improved and the air leakage diminished gradually. The patient could be weaned successfully from mechanical ventilation in three days.

Figure 1. *CXR with initial right-sided pneumothorax*

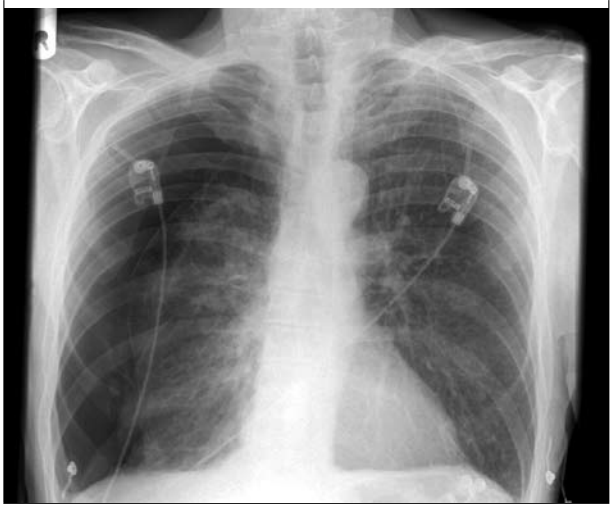


Figure 2. *CXR after thoracostomy tube insertion with resolution of the right-sided pneumothorax*

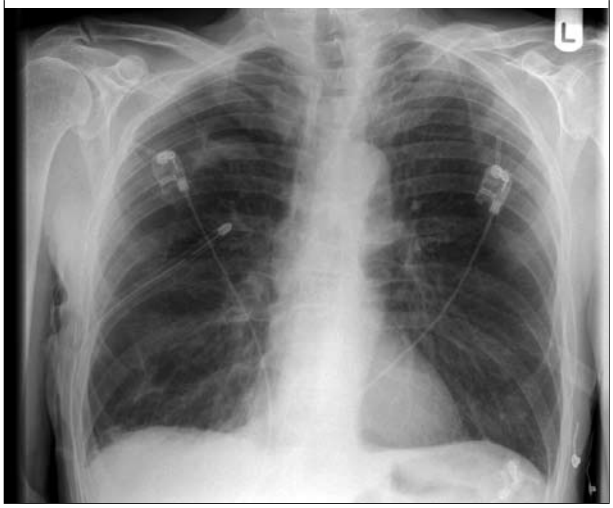


Figure 3. *CXR with recurrent right-sided pneumothorax, despite thoracostomy tube in place*

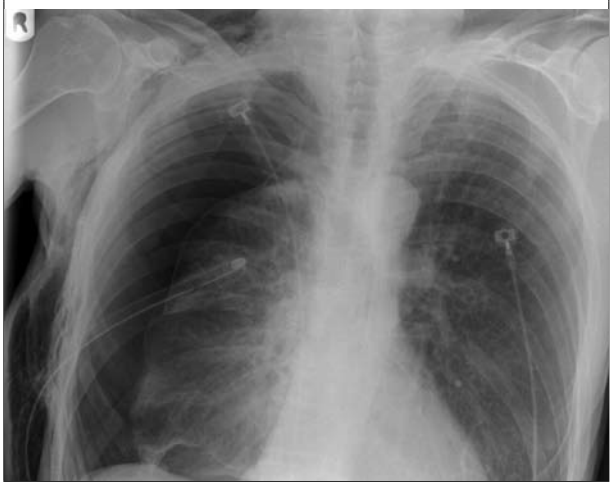
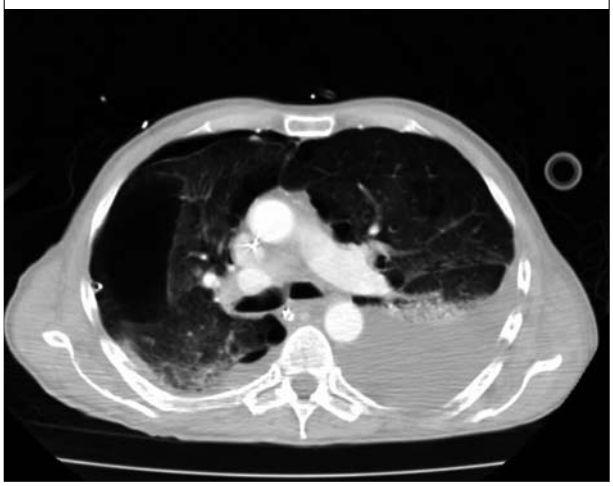


Figure 4. *CT scan with giant bullae and anterior pneumothorax after insertion of a second thoracostomy tube*



CONCLUSIONS

Pneumothorax is classified as either spontaneous, iatrogenic or traumatic.[1]
Primary spontaneous pneumothorax occurs in persons without clinically apparent lung disease with an incidence of 1.2 to 6 cases per 100,000 among women and between 7.4 to 18 cases per 100,000 population in men.[2] Smoking cigarettes increases the risk of primary spontaneous pneumothorax.[3] The term 'secondary spontaneous' means that the pneumothorax is a complication of pre-existing lung disease. Although patients with primary spontaneous pneumothorax do not have clinically apparent lung disease, bullae are often found during VATS or thoracotomy as in our present case.[4] CT studies of the chest have shown that ipsilateral bullae are common findings in smoking patients with spontaneous pneumothorax. Cases of spontaneous pneumothorax due to giant bullae have been previously reported and can be very difficult to treat.[5] Radiological diagnosis of bullous disease in a previously healthy patient can be difficult and may easily be missed.[6]
In our case, the patient developed a tension pneumothorax even with a thoracostomy in place. The patency of the thoracostomy was double-checked and found to be draining. The tension pneumothorax was most likely caused by a loculated ventral bullous pneumothorax, which did not drain through the primary thoracostomy as was shown on CT scan. Aggressive management to prevent circulatory collapse and respiratory failure and early surgical consultation are warranted if recurrent pneumothorax occurs after primary thoracostomy. If this uncommon situation is recognised, an adverse outcome can be prevented.

ACKNOWLEDGEMENTS

We would like to express our special thanks to Steffen van Leeuwen and Jos van Die for their assistance.

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ANSWER TO PHOTO QUIZ (ON PAGE 350)

THE ECG IN HYPOTHERMIA: OSBORN WAVES

DIAGNOSIS

The ECG (*figure 1*) showed atrial fibrillation with a ventricular rhythm of 110 beats/min and prolonged conduction intervals. The J waves or Osborn waves (arrows) were striking. The patient was actively rewarmed under haemodynamic surveillance without complications. Six hours after presentation his body temperature had risen to 35°C. The ECG showed normal sinus rhythm without the Osborn waves (*figure 2*).

The next day it became clear that the patient had used cocaine, which had probably caused the initial mental disturbance.

Hypothermia (body temperature <35°C) can be divided into three categories (mild between 32 and 35°C, moderate between 28 and 32°C, and severe <28°C). This classification is important for assessing the risk of complications. The most serious complications occur with temperatures below 28°C and consist of hypotension, pulmonary oedema, areflexia, bradycardia, ventricular fibrillation and asystole.[1]

Hypothermia instigates typical changes on the ECG as a consequence of artefacts during shaking and because of the retarded conduction through the cardiac tissue. This is responsible for the prolonged conduction times measured. Elevation of the J point is also possible and can be seen as the characteristic Osborn waves, named after J.J. Osborn who initially described them. They are the result of a more prominent transient outward potassium current resulting in a transmural voltage gradient in the epicardium, more pronounced under hypothermic conditions.[2] Description of the exact mechanism is beyond the scope of this article. Osborn waves are most distinct in the precordial and inferior leads and disappear after normalisation of the body temperature. They are a characteristic finding in hypothermia but also occur in other conditions such as hypercalcaemia.[2]

The presence of Osborn waves is not associated with a higher mortality in contrast to the presence of atrial fibrillation and the absence of shivering artefacts.[3]

CONCLUSION

J waves or Osborn waves on the ECG in accidental hypothermia.

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Figure 1. *ECG during hypothermia (29°C) - note atrial fibrillation and Osborn waves (arrows)*

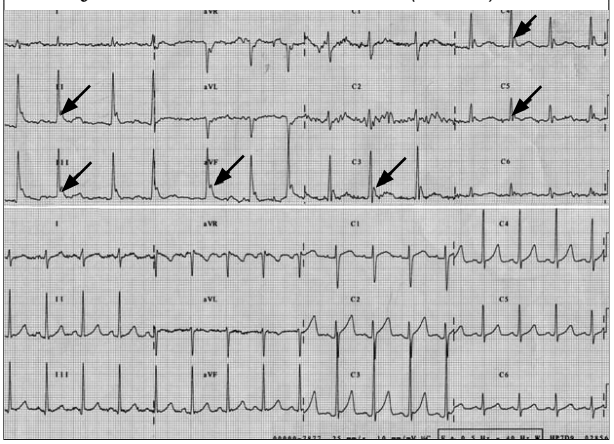
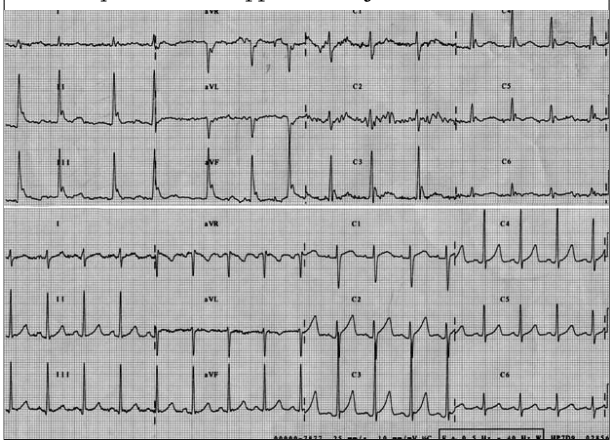


Figure 2. *ECG in normothermia: restoration of normal sinus rhythm and disappearance of Osborn waves*



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ABOUT THE COVER

Love me tender

Marjoke Schulten

Marjoke Schulten (1970) attended the Academy of Art in Rotterdam where she graduated in Free Graphics. She mainly focussed on lithographic and etching techniques. These techniques have been expanded with mixed high-pressure print techniques.

After graduation she moved to a workroom which used to be a school building on Noorder Island in Rotterdam. Nowadays, this place has grown into a full graphic studio.

The prints she creates have a happy expression and at the same time an astringent taste. She tries to image the field of tension between capability and inability. Individuals trying to achieve a goal which will be an illusion. Suddenly, when the goal is in sight, the road leading to it seems to be blocked. On their way to reaching the goal these persons will be confronted with fear, visions, dreams and desires. In addition to several individual expositions, Schulten has exhibited her work at many group expositions in the Netherlands and abroad.

An original print is available at a price of € 200 and can be ordered from Galerie Unita, Beek-Ubbergen, the Netherlands, e-mail: galerie-unita@planet.nl, www.galerie-unita.com

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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.
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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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