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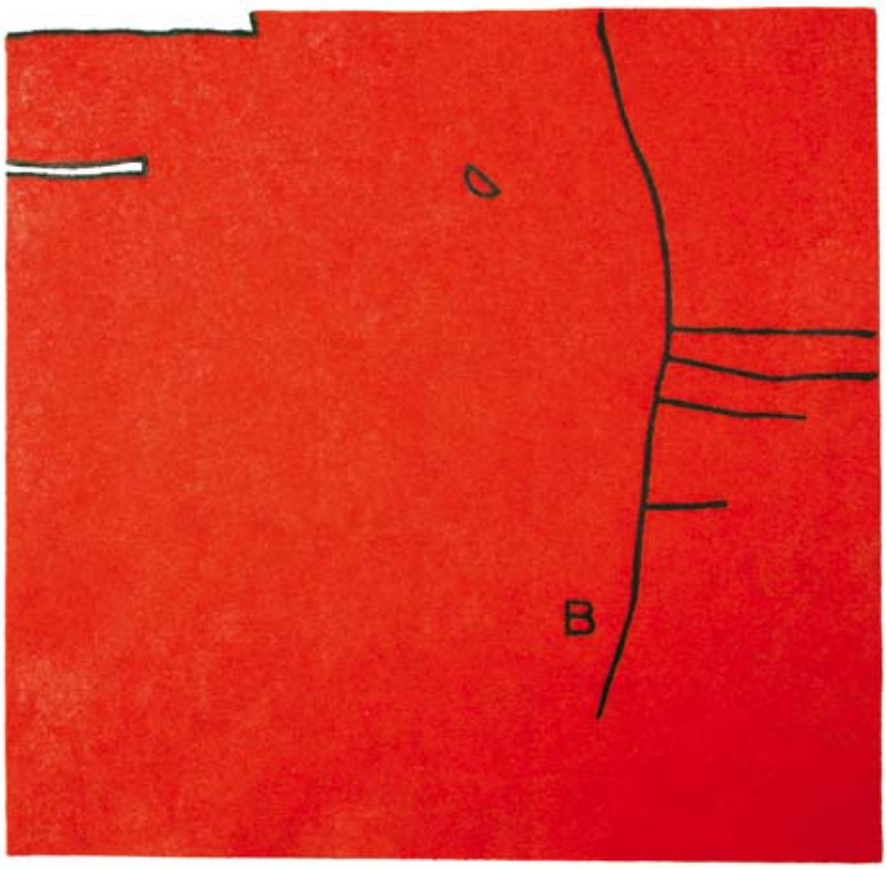

The art of autopsy
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Thiazolidinedione derivatives
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Chronic hepatitis B virus infection
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Helicobacter pylori
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Polycystic liver desease

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VAN ZUIDEN COMMUNICATIONS

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EDITORIAL

The art of autopsy – time for a renaissance

R.G.J. Westendorp

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The overwhelming majority of people now die in old age. From a medical perspective the end of life is paved with comorbid conditions that over decades of time have led to multiple organ damage and failure of complex systems. Clinicians who are responsible for (old) patients are in need of detailed information on the structural status and remaining function of the failing body to guide their therapies. In this issue of the Journal, colleagues from the Department of Geriatric Medicine in Nijmegen report on clinical decisions that, often in the absence of sufficient information, appeared disputable when the outcomes of autopsy became available.[1] The authors should be praised for having exposed the outcomes of their professional work to us. This is especially true as the art of autopsy is rapidly fading and this type of comparative study may not be doable in the future. There is no question that for some of their patients the authors would have decided otherwise if the appropriate information had been available during life. Hence, it is critical to understand why doctors often lack this crucial information on structure and function of the failing body to guide their clinical decisions. And, why are we not bothered by such ignorance?

Nowadays, imaging techniques such as computerised tomography (CT) and magnetic resonance imaging (MRI) can easily be applied during life and seem to have made the pathological examinations after death unnecessary. Structural data from CT and MRI can also be combined with functional studies and it is suggested that with this combination in hand clinicians have all the critical information for decision-making. And, without doubt, this is far more valuable than having this information after death. But quite often in the old, in whom virtually all organs are damaged and only patchy structural and functional information is available, we do not fully understand the complex interactions that are at play. Might it be that in some of our patients our inference is false? Shouldn't there be a regular check whether we were correct in our reasoning, as a kind of quality control? And what if whole body scanning and total function testing becomes undoable in frail and diseased elderly? A situation that is even more complicated when patients are critically ill, bound to a ventilator and have a pacemaker implanted.

Access to CT and MRI has had a groundbreaking impact on the diagnostic abilities of clinical medicine and it is therefore not surprising that both inventions have led to a Nobel Prize. The techniques were both pioneered on the brain. The size of the scull and the fact that brains do not move makes the head a perfect body structure to start with. But perhaps this choice can also be explained because the brain was one of the latest 'untouchable' organs, at least during life. This frustrating ignorance of what was going on in the brain is most likely not different from the feeling that in ancient time has led to performing autopsies. Did the earliest dissections serve to reveal the secret of life? Without doubt Michelangelo must have used autopsy to better paint and sculpture his figures. Anatomy and physiology could only flourish by dissections performed by masters as Versalius and Harvey. All of this now seems history, but it is essential to realise that nowadays techniques as CT and MRI have not replaced the pathological examination of the brain. It has only recently been shown that a large proportion of old people without cognitive impairment and normal CT and MRI of the brain have significant Alzheimer pathology at autopsy. The modern techniques have missed this critical observation and are as yet unable to reveal this type of structural damage. And how should we interpret the white matter hyperintensities on MRI that are so closely associated with Alzheimer dementia and depression? The underlying pathology has still not been fully determined, as combined studies of MRI and pathology are so scarce. The modern techniques show us far more abnormalities than we are currently able to interpret.

The ageing body is filled with yet unresolved mysteries. The structural and functional basis of the failing heart and kidney in old age is largely unknown. Why is it that osteoporosis of the radius does not synchronise with osteoporosis of the back? Some parts of the body could better be described as unknown territories. Muscles have hardly been explored

in old age and muscle weakness has not even been given a name other than 'normal ageing'. Poor muscle strength can in part explain why people fall, suffer from hip fractures, or develop respiratory insufficiency. There is emerging evidence that muscles of older people are deficient of 'pericytes', organ-specific stem cells that are necessary for the repair of damaged tissue. Specific expression of proinflammatory cytokines may contribute to muscle weakness in animal models but there are hardly any data in man to support such a malleable biological mechanism.

Let our ignorance of disease in old age serve as a catalyst for the renaissance of autopsy.

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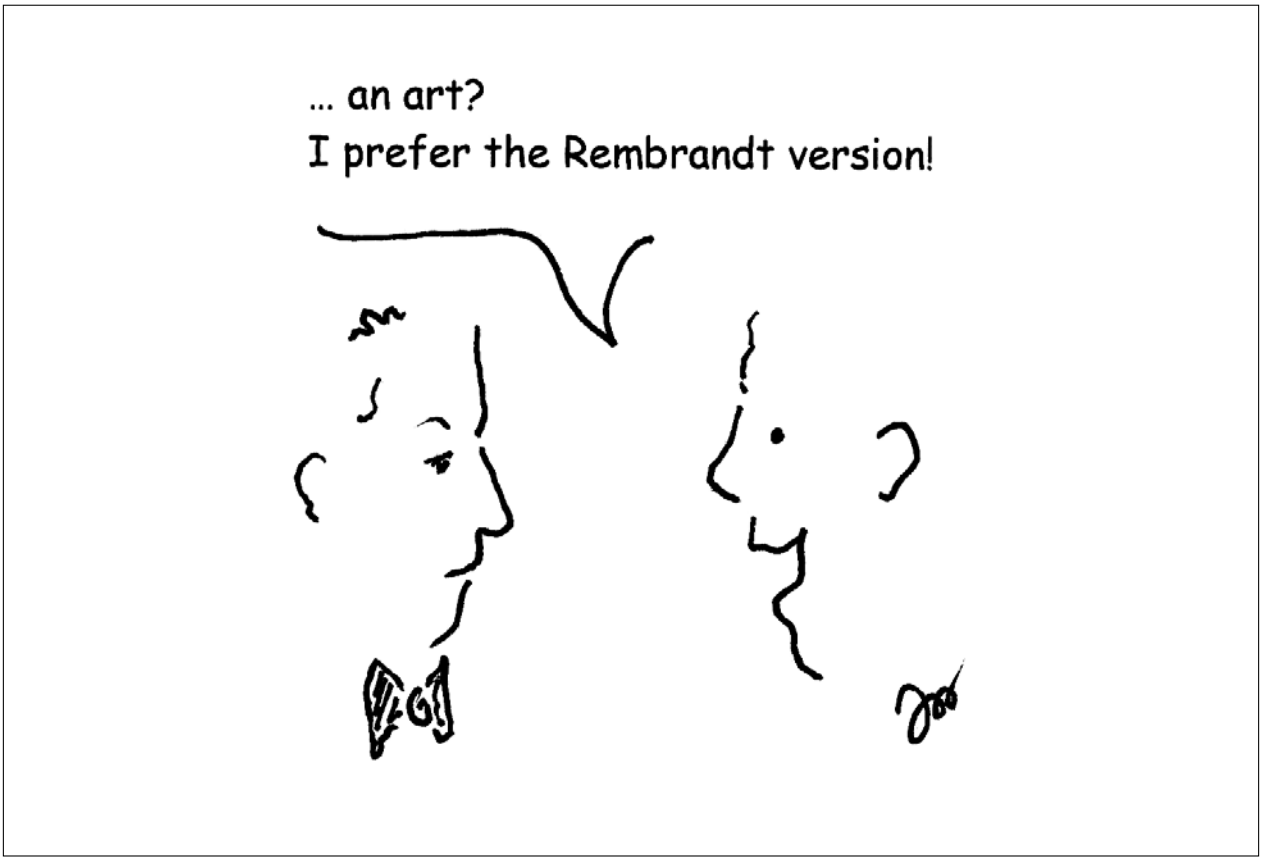
1. Aalten CM, Samson MM, Jansen PAF. Diagnostic errors in geriatric medicine; why we should continue to have autopsies. Neth J Med 2006;64(6):186-90.



Westendorp. The art of autopsy.

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REVIEW

Thiazolidinedione derivatives in type 2 diabetes mellitus

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ABSTRACT

In Europe, the thiazolidinedione derivatives pioglitazone and rosiglitazone have been approved for the treatment of type 2 diabetes mellitus either as monotherapy for patients with intolerance or contraindications to metformin or in combination therapy. This class of drugs seems particularly suited for obese patients, but is currently not considered as a first choice for monotherapy. The efficacy with respect to blood glucose lowering is comparable with sulphonylurea (SU) derivatives and with metformin. Long-term data with respect to efficacy and side effects are still limited.

KEYWORDS

Combination therapy, monotherapy, pioglitazone, rosiglitazone, thiazolidinedione derivatives, type 2 diabetes mellitus

INTRODUCTION

Pioglitazone and rosiglitazone, two oral blood glucose lowering drugs for the treatment of type 2 diabetes mellitus, have been marketed in the Netherlands since 2000. Both belong to the class of thiazolidinedione derivatives (TZDs), also referred to as glitazones or peroxisome proliferator-activated receptor (PPAR)-γ agonists. It should be realised that compounds other than the TZDs can also stimulate the PPAR-γ receptor. In this review the term TZDs will be used.

The TZDs represent a new class of drugs with a new mechanism of action. In Europe, TZDs have been approved for type 2 diabetes mellitus, particularly for overweight patients who are inadequately controlled by diet and exercise alone, for whom metformin is inappropriate because of contraindications or intolerance. TZDs have also been approved for use in combination therapy. Unlike the situation in the USA, TZDs are not approved, but even contraindicated for use in combination with insulin in Europe. From the day of approval onwards, there has been discussion concerning the exact place of TZDs within the pharmacotherapy of type 2 diabetes mellitus. Different views have resulted in differences in guidelines and treatment standards. The lack of data on long-term clinical studies with 'hard' endpoints (mortality and new macrovascular events) definitively plays an important role in this discussion. Recently, the first outcome study was published (the PROactive study),[1] but this study has also raised several questions.[2-5]

With respect to glucose regulation, TZDs do not seem to be superior to the conventional drugs metformin or sulphonylurea (SU) derivatives. Therefore, potential additional benefits but also side effects of TZDs, such as fluid retention and weight gain, are important in the discussion on the position of this class of drugs in the pharmacotherapy of type 2 diabetes mellitus.

In this review the following topics will be discussed: pathophysiology of type 2 diabetes mellitus, available drugs, pharmacology and mechanism of action of TZDs, efficacy, side effects and contraindications of TZDs, use during pregnancy and lactation and some future perspectives. Finally, a guide to the use in clinical practice is provided.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

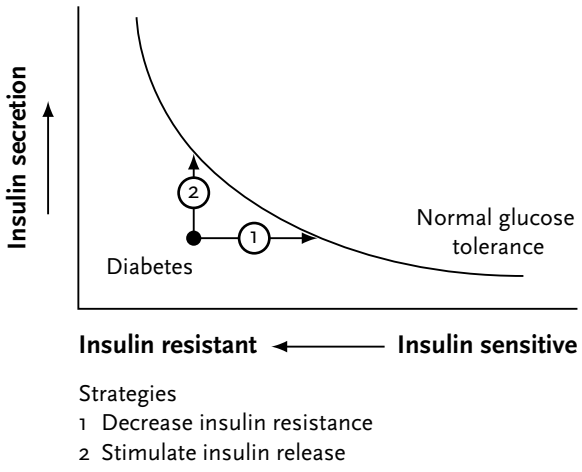
The pathogenesis of type 2 diabetes mellitus is complex and has only been partially clarified. Clearly, the capacity of the pancreas to produce insulin is reduced. On diagnosis, β-cell function is generally reduced to approximately 50% of what is considered normal. In addition to this defect in insulin secretion, there is a reduced sensitivity to the

#P. Smits was not involved in the handling and review process of this paper.

effect of insulin on the target organs (insulin resistance). Insulin resistance is closely related to obesity. Once a state of chronic hyperglycaemia has been reached (diabetes), a number of secondary alterations take place that, although in themselves not the cause, do lead to an additional increase in both insulin resistance and β-cell dysfunction. The term glucose toxicity is used to refer to these secondary defects. *Figure 1* shows the normal relationship between insulin secretion and insulin sensitivity.

Recent data suggest that an increase in fat mass (obesity) results in a reduction in the effect of insulin on skeletal muscles and the liver.[6] With respect to obesity, not only the absolute amount of fat is important, but also body fat distribution. In particular, visceral fat and fatty tissue in skeletal muscle and liver are crucial in the development of insulin resistance. When insulin resistance develops in a subject who already has a (largely genetically determined) β-cell defect, plasma glucose will rise and diabetes will occur.

Figure 1. *Normal relationship between insulin sensitivity and insulin secretion (once insulin secretion can not match insulin resistance, diabetes will develop)*



DRUGS, PHARMACOLOGY AND MECHANISM OF ACTION

Drugs

The prototype of the TZD class of drugs, ciglitazone, was first described in 1982.[7] This agent did not reach the market due to insufficient efficacy and an unfavourable side effect profile. The first marketed TZD was troglitazone. Apart from the thiazolidine-2-4-dione group, troglitazone also contains an α-tocopherol group (analogue to vitamin E). When developing troglitazone the idea was to develop a drug that would inhibit the peroxidation of lipids in addition to having a favourable effect on insulin resistance (thiazolidine group). Troglitazone was taken off the market worldwide in March 2000 due to severe liver toxicity, sometimes with fatal consequences.[8] At present, pioglitazone and rosiglitazone are available on the Dutch market.

Pharmacokinetics

The bioavailability of the TZDs following oral intake is high and once absorbed, TZDs are largely bound to protein in the plasma (>99%). Both pioglitazone and rosiglitazone are mainly metabolised by CYP2C8 and to a small degree by CYP2C9. With normal liver function, the elimination half-life of pioglitazone and rosiglitazone is 5 to 6 and 3 to 4 hours, respectively. The two active metabolites of pioglitazone have an elimination half-life of 26 to 28 hours, which thus facilitates the single daily dose of pioglitazone. A once-daily dosage schedule is also recommended for rosiglitazone.

Pharmacodynamics

The mechanism of action of the TZDs is based on binding to the PPAR-γ receptor.[9] PPAR-γ belongs to the group of nuclear transcription factors. Transcription factors affect the level of expression and thus the activity of various genes. By making some genes more and others less active, transcription factors affect cellular function. In humans, PPAR-γ is mainly expressed in fat cells and this is where the TZDs appear to act primarily. Unlike most other drugs, TZDs do not act by binding to membrane receptors, but by binding to transcription factors in the cell nucleus.

In response to PPAR-γ receptor activation, the expression of hundreds of genes in the target cells changes. The net effect in fat tissue is that (pre)adipocytes differentiate. As a consequence, fat tissue takes up triglycerides more easily while lipolysis is inhibited. Subsequently, the level of circulating free fatty acids decreases, which will indirectly promote glucose uptake in skeletal muscle. After a number of weeks, this results in a decrease in insulin resistance. Other mechanisms may also play a role in improving insulin sensitivity.[9]

Based on this mechanism of action, it is clear that fat mass will increase during treatment with TZDs; in particular the quantity of subcutaneous fat will increase. Treatment with TZDs ultimately leads to an average weight gain of 2 to 4 kg. Interestingly, this weight gain parallels the decrease in insulin resistance. This can be explained by the fact that TZDs reduce the quantity of fat in nonfatty tissues such as the liver and skeletal muscles. So, fat redistribution rather than an increase in fat mass occurs.[6] The net effect of TZDs is a reduction in peripheral insulin resistance; improvement of insulin-stimulated glucose uptake in peripheral tissues, in particular in skeletal muscle. Insulin resistance in the liver is also diminished, resulting in a reduction of endogenous glucose production.[10,11]

EFFICACY

Approved therapeutic indications

According to the official text, pioglitazone and rosiglitazone have been approved as monotherapy for the treatment of patients with type 2 diabetes mellitus, particularly overweight patients who are inadequately controlled by diet and exercise and for whom metformin is inappropriate because of contraindications or intolerance. TZDs are also approved for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite the maximum tolerated dose of oral monotherapy with either metformin or sulphonylurea:

- in combination with metformin particularly in overweight patients;
- in combination with a sulphonylurea derivative only in patients who show intolerance to or a contraindication to metformin.

Finally, rosiglitazone is approved as triple oral therapy in combination with metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

It should be mentioned that in clinical studies with TZDs the following exclusion criteria have generally been used: planned revascularisation procedure, symptomatic heart failure, cruric ulcers, peripheral gangrene or rest pain in the leg, haemodialysis, liver function disorder (alanine transaminase (ALAT) level >2.5 times the upper limit of normal), renal function loss, anaemia and diabetic retinopathy, neuropathy or nephropathy.

Efficacy

The inter-individual differences in the blood glucose lowering response to TZDs are great. Theoretically, patients with a prominent insulin resistance (marked abdominal obesity, fatty liver, high endogenous insulin concentrations) are more suited to TZD therapy than to treatment with sulphonylurea derivatives, but there are no clinical trials to support this notion. TZDs are also effective in other disorders associated with insulin resistance, such as polycystous ovary syndrome[12] and nonalcoholic fatty liver disease,[13] but this has not resulted in specific approved indications.

TZDs (monotherapy or combination therapy) *vs* placebo

Effects on glycemic control

Monotherapy

In two randomised, double-blind and placebo-controlled studies with pioglitazone, the HbA_{1c} level dropped by 1.05% (30 mg) in comparison with placebo[14] and by 0.8% (30 mg) and 0.9% (45 mg).[15] Randomised, double-blind and placebo-controlled studies using rosiglitazone showed a decrease in HbA_{1c} levels of 1.5% (4 mg twice daily) after 26 weeks of treatment in comparison with placebo.[16,17]

Combination therapy

In placebo-controlled studies of the addition of rosiglitazone (4 or 8 mg/day) to metformin, HbA_{1c} level dropped by 1.2% with 8 mg in comparison with placebo.[18,19] In patients who were inadequately controlled by the combination glibenclamide/metformin, the addition of rosiglitazone for 24 weeks reduced the HbA_{1c} level by 1% compared with placebo treatment.[20] Comparable results have been reported for pioglitazone.[21] In summary, TZDs provide an average HbA_{1c} reduction of 0.7 to 1.5% on top of metformin therapy.

Comparative studies with other oral blood glucose lowering drugs

Sulphonylurea derivatives

Compared with gliclazide, 52 weeks of treatment with pioglitazone (45 mg) resulted in a similar reduction in HbA_{1c}, which was 1.4% for both drugs.[22] The average reduction in the fasting blood glucose value was significantly greater with pioglitazone than with gliclazide (2.4 *vs* 2.0 mmol/l). In another study, the effects of pioglitazone and gliclazide were compared for two years in 567 patients.[23] In patients who had received pioglitazone the target value of the HbA_{1c} was reached more often than in the patients who had received gliclazide (47.8 *vs* 37.0%). In a similar study, the efficacy of metformin/pioglitazone (from 15 to 45 mg) was similar to metformin/gliclazide (HbA_{1c} reduction of 1% in both groups).[24]

Metformin

In one study, 45 patients with type 2 diabetes mellitus, who had not previously been treated with drugs, were randomised to treatment with rosiglitazone (4 mg twice daily), metformin or placebo.[25] After 26 weeks, both metformin and rosiglitazone had significantly reduced the HbA_{1c} in comparison with placebo. These observations were confirmed in another study.[26]

Several randomised studies have compared pioglitazone and metformin and showed a comparable fall in HbA_{1c} level.[27-31]

Pioglitazone vs rosiglitazone

A meta-analysis of studies on the effects of TZDs on cardiovascular risk factors concluded that pioglitazone and rosiglitazone have comparable effects on blood glucose control and on body weight.[32] In line with this meta-analysis, a recent study showed a similar effect on glucose regulation in a direct comparison between the two TZDs.[33]

Thus, with respect to the blood glucose lowering effect, pioglitazone and rosiglitazone are comparable and similar in efficacy compared with metformin and SU derivatives.

Effects on cardiovascular risk factors (non-glycemic effects)

Besides their effect on glucose metabolism, TZDs have also been shown to affect cardiovascular risk factors,

including lipids, blood pressure and inflammatory and fibrinolytic parameters.[34-36] These effects are probably linked to changes in gene expression.

Effects on lipids

A literature review on the effects of pioglitazone and rosiglitazone on blood lipids summarises that pioglitazone has a stronger effect on triglycerides, total cholesterol and LDL cholesterol than rosiglitazone.[37] Pioglitazone leads to a reduction in triglyceride concentration, an increase in HDL cholesterol concentration, and a neutral effect on LDL and total cholesterol concentrations. Rosiglitazone raises HDL, LDL and total cholesterol concentrations, and has a neutral effect on the triglycerides.[38] A meta-analysis of randomised placebo-controlled studies of pioglitazone or rosiglitazone shows that pioglitazone has a stronger effect on the serum lipids than rosiglitazone.[32] In general, the LDL composition tended towards a less atherogenic pattern in the studies with pioglitazone than in the studies with rosiglitazone.

Two randomised, double-blind studies have been published in which the effects of pioglitazone and rosiglitazone on blood lipids were compared.[33,39] The effects of these TZDs on lipids differed. The concentration of triglycerides was reduced by pioglitazone, whilst it increased with rosiglitazone. Furthermore, the increase in the concentration of HDL cholesterol was more pronounced whereas the increase in LDL cholesterol concentration was smaller with pioglitazone compared with rosiglitazone. In the second study the effects of pioglitazone and rosiglitazone were compared in patients with type 2 diabetes mellitus and the metabolic syndrome who had already been treated with glimepiride.[39] The results showed that the lipid spectrum was significantly more reduced when taking pioglitazone compared with rosiglitazone.

Although pioglitazone thus appears to have a more beneficial effect on lipids, it should be noted that the patient characteristics in the studies with pioglitazone significantly differed from those of the rosiglitazone studies. Furthermore, the quantitative effects of TZDs on lipid concentrations are limited,[40] and it is important to realise that TZDs are no alternative for lipid-lowering drugs.

Effects on blood pressure

Both pioglitazone and rosiglitazone induce a small reduction in blood pressure, in particular of the diastolic blood pressure.[41-43] In a meta-analysis of four double-blind studies comprising 3700 patients with type 2 diabetes mellitus a comparison between the effects of pioglitazone, metformin and gliclazide on cardiovascular risk factors was made.[44] The blood pressure was reduced to some extent by all treatment modalities, but the reduction with pioglitazone was more pronounced (about 1.5 mmHg). There were no differences in hospital admissions for cardiac or cerebrovascular events, mortality or the occurrence of heart failure.

Effects on inflammatory and fibrinolytic factors

Both pioglitazone and rosiglitazone reduce the concentrations of circulating inflammatory factors such as C-reactive protein and interleukin 6,[42] and affect the fibrinolytic system, thereby causing, among other things, a reduction in tissue plasminogen activator (t-PA).

All these 'nonglycaemic' actions of TZDs hold the promise that TZDs may have positive effects on cardiovascular endpoints, beyond their glucose lowering effect. The final proof for this claim needs to come from cardiovascular outcome studies. One outcome study has recently been published,[1] others are ongoing.[45,46] In addition, a number of studies have yielded positive results on surrogate cardiovascular endpoints. These comprise endothelial function,[47,48] changes after coronary interventions and intima-media thickness.[49,50]

The PROactive study

The 'PROspective pioglitAzone Clinical Trial In macroVascular Events' (PROactive) study has recently become available through internet reports, symposia and has been published in the Lancet.[1] Being the first outcome study, the study has been viewed with considerable interest. PROactive is a randomised double-blind study of 5238 patients with type 2 diabetes mellitus *and* macrovascular disorders in which the efficacy of pioglitazone (45 mg) in reducing the occurrence of new macrovascular events or death was compared with placebo.[51] The average age of the patients when the study was initiated was 61.8 years, most of them were male (66.1%) and 75.4% had hypertension. By definition, all patients had had a cardiovascular event, thus this was, in fact, a secondary intervention setting. The average body mass index (BMI) was 30.9 kg/m^2. The study drug was given on top of the patients usual antidiabetic medication and in one third of the cases in combination with insulin. This design was chosen to assess the effect of pioglitazone on cardiovascular disease *independent* of its effects on lowering blood glucose.

The study results show that pioglitazone treatment was associated with a nonsignificant 10% decrease in the primary, predefined, composite endpoint[51] and a significant 16% reduction in event rate of any of total mortality, nonfatal myocardial infarction or stroke (secondary endpoint). The claim of the paper 'pioglitazone reduces mortality, myocardial infarction and stroke' has, however, met considerable criticisms,[2-4,37] which renders it difficult to translate the results to clinical practice. The major limitations of the study are its population, its design and the side effects. Firstly, the population had a relatively high rate of smoking and a low rate of statin use (43%, given the setting of secondary prevention this should ideally have been 100%), resided in countries with relatively low access

to modern healthcare facilities and, perhaps in line with these characteristics, the population had a higher event rate than expected. This resulted in a more rapid conclusion of the trial than anticipated.

Although the design of the study aimed at similar glycaemic control in both treatment arms, the pioglitazone-treated patients had a better glycaemic control (mean difference in HbA_{1c} 0.5%), which, according to some,[4] may in fact largely explain the beneficial effect. Finally, the positive results were tempered by the increased prevalence of peripheral oedema and congestive heart failure[2] and by the substantial weight gain (average per patient 4 kg).

DIFFERENCES BETWEEN PIOGLITAZONE AND ROSIGLITAZONE

Pioglitazone and rosiglitazone were approved at about the same time and there are more similarities than differences between the two drugs. Rosiglitazone is administered in a dose of 4 mg once daily, which can be increased to 8 mg once daily or (preferably) 4 mg twice daily, whilst pioglitazone is administered once daily in a 30 mg dose. In fact, 30 mg pioglitazone is considered to be equipotent with 6 mg of rosiglitazone. Several studies with pioglitazone have been carried out with the 45 mg dose, mostly in American patients, whilst European studies often used 30 mg doses. Two studies have compared pioglitazone and rosiglitazone with respect to effects on lipids (see above).

SIDE EFFECTS, CONTRAINDICATIONS, INTERACTIONS, USE DURING PREGNANCY AND LACTATION

Hypoglycaemia, one of the main side effects of oral blood glucose lowering drugs, does not occur with TZDs, because they do not affect the secretion of insulin. Hypoglycaemia can occur in combination with other drugs, but in that case it is not due to the TZDs.

Although the hepatotoxicity of troglitazone has clearly been demonstrated,[8] it has been proven that rosiglitazone and pioglitazone are less associated with hepatotoxicity. In fact a slight improvement in liver enzyme values usually occurs, probably as a result of the reduction in the amount of liver fat.[6] Two large retrospective analyses showed that the use of pioglitazone or rosiglitazone over a period of one to two years was not associated with an increase in liver failure or hepatitis, in comparison with other oral blood glucose lowering drugs.[52,53] This does not detract from the fact that severe liver function disorders have been reported and described in the literature during the use of both agents,[54-56] including irreversible, lethal liver damage as a result of pioglitazone.[53] No publications have appeared on rosiglitazone in this respect, but the summary of product characteristics (SPC) text does state that a fatal outcome has been reported in rare cases. The Dutch Lareb Pharmacovigilance Centre has also registered reports of increases in the plasma concentration of liver enzymes. The SPC text still advises against administering TZDs to patients with an ALAT concentration that is increased to >2.5 times the upper limit of normal, and against prescribing it to patients who developed liver function disorders to another TZD.

The most important side effects of the TZDs are fluid retention and an increase in subcutaneous fat, which both contribute to the above-mentioned weight gain. It is not definitively known which part of weight gain is caused by fluid and which by fat. A recent study suggests that fluid accounts for as much as 75% of body weight increase,[57] although others have estimated fat as quantitatively the most important.[6] The quantity of fat in the visceral compartment and ectopic fat (liver and skeletal muscle) remain unaltered following the use of TZDs, or are even reduced.[6] The increase in body weight due to TZDs usually amounts to less than one kilogram after 16 weeks in people without diabetes, but it can be as much as 3 to 4 kg in patients with diabetes mellitus, particularly in combination with sulphonylurea derivatives or insulin. The larger the drop in HbA_{1c}, the larger the weight gain was.[58]

The pathogenesis of fluid retention under the influence of TZDs is largely unknown, and appears multifactorial.[39,43] Fluid retention can lead to oedema, thereby leading to heart failure.[59] The decrease in haematocrit level is also considered to be a result of the increase in plasma volume. In some patients this can result in frank anaemia, although not to a clinically relevant degree. Fluid retention, and the related increased risk of heart failure, occurs in particular when TZDs are combined with insulin. This combination is therefore contraindicated by the European Agency for the Evaluation of Medicinal Products (EMEA). Although fluid retention does occur with the present indications even when the contraindications are taken into consideration, the risk of clinical heart failure is limited, occurring in only a few percent of patients.[59] It should be realised that patients with type 2 diabetes are often elderly, with substantial comorbidity, related or not related to the diabetes. For example, caution will be required in dosing patients with hypertension, coronary heart disease, left ventricular hypertrophy, heart failure, aged >70 years, diabetes mellitus for more than ten years, use of insulin and chronic renal failure.[59]

In view of the fluid retention side effect, all forms of heart failure (New York Heart Association [NYHA] classes I to IV) are a contraindication for using TZDs, as is the combination with insulin. TZDs should be discontinued at the first signs of heart failure. Liver enzyme disorders are also a contraindication for the use of TZDs. For this

reason the plasma concentrations of gamma glutamyl transferase (γGT) and of ALAT should first be determined prior to treatment. In the case of fatty liver disease (hepatic steatosis), serum concentration of the ALAT enzyme is often already raised. In those cases, treatment with TZDs may improve liver steatosis. In practice, therefore, one might consider a TZD in the case of liver function disorders as a result of steatosis, as long as the liver enzymes are strictly monitored. The EMEA recently decided that the obligatory two-monthly liver function check-up could lapse. The advice to check liver function prior to therapy remains unchanged.

Pioglitazone is metabolised via CYP2C8, 3A4 and 1A1, rosiglitazone via CYP2C8 and 2C9. In theory, drug interactions are possible with drugs that have an inhibitory effect on CYP2C8, 2C9, and in the case of pioglitazone, on CYP3A4. Trimethoprim is an inhibitor of CYP2C8 and there is evidence that the chronic use of trimethoprim leads to a reduction in the clearance of rosiglitazone in healthy volunteers.[60,61] A reduction in the clearance of rosiglitazone was also observed in healthy volunteers during an interaction study with ketoconazol.[62] The reductions were 30 to 40% and 47% respectively. These interactions can be expected to lead to a drop in the blood glucose concentration in patients with type 2 diabetes mellitus treated by TZDs.

Rifampicin is a strong inducer of several CYP enzymes and in an interaction study with rosiglitazone, rifampicin doubled the clearance of rosiglitazone in healthy volunteers.[61,63] Therefore, this combination leads to a reduction in the effect of rosiglitazone.

On theoretical grounds, the simultaneous use of an NSAID and pioglitazone or rosiglitazone can increase the risk of oedema. Combining a TZD with insulin can – also on theoretical grounds – increase the risk of heart failure. Finally, gemfibrozil is known to increase[64] the plasma concentration of rosiglitazone.[65]

TZDs are contraindicated during pregnancy (class C evidence) based on the observations of growth retardation in animal studies.

FUTURE PERSPECTIVES

TZDs are not superior to other oral blood glucose lowering drugs with respect to their glycaemic effect. As such, conventional oral therapy will continue to be important in the treatment of type 2 diabetes mellitus as will combination therapy. A recent study from general practitioners in the Utrecht area of the Netherlands showed that standardised, protocol-based conventional care (including lifestyle education, oral medication and insulin), and the deployment of health visitors led to an appropriate glycaemic control for the majority of patients.[66-68]

The results of the first cardiovascular outcome study (PROactive) suggest that one of the TZDs has potential beneficial effects on cardiovascular disea se, but because of several limitations as described in the paragraph above, translation to clinical practice is limited. Even with these new data, metformin remains the first-choice drug because much more experience has been obtained with metformin, because metformin does not lead to weight gain and because the drug is much cheaper. According to this line of reasoning, TZDs will then become an alternative second-choice drug in patients with cardiovascular disease not being heart failure.[5] However, it is unclear whether the PROactive study results[1] can be extrapolated to the current population of type 2 diabetes, which is largely treated with statins or those without cardiovascular disease. In addition, it is unclear whether the results obtained with pioglitazone are drug specific or a class effect of TZDs. The results of other ongoing outcome studies[45-46] will hopefully reveal more information on this topic.

TZDs may also have a protective effect on the β-cell, either due to a reduction in the concentration of free fatty acids (reduced lipotoxicity) or via other mechanisms. In practice, this should result in a longer period on (mono)therapy before secondary failure. In the ADOPT (A Diabetes Outcome Progression Trial), the time to treatment failure will be compared between rosiglitazone, metformin and glibenclamide.[69] The results will become available by the end of 2006.

CURRENT PLACE OF TZDS IN DIABETES TREATMENT

At present, pioglitazone and rosiglitazone are approved[70] for the treatment of type 2 diabetes mellitus, either as monotherapy for patients (particularly in cases of obesity) who do not tolerate metformin or have a contraindication, or as combination therapy for patients who are already taking a sulphonylurea derivative and/or metformin. This implies that TZDs are not first-choice monotherapy.

With respect to the blood glucose lowering effect, TZDs are comparable with sulphonylurea derivatives and with metformin. The arguments for choosing one drug in preference to another will be addressed point-by-point. The drug acarbose will not be taken into consideration because the balance of efficacy *vs* side effects is considerably less favourable than with metformin and sulphonylurea derivatives. Neither will the meteglinides be taken into consideration because repaglinide is not reimbursed in the Netherlands and nateglinide is not marketed in the Netherlands.

Monotherapy

Metformin is the first choice for patients with type 2 diabetes mellitus and obesity who are insufficiently regulated by diet and lifestyle advice. The results of the

UKPDS study show that, in comparison with conservative treatment, intensive treatment with metformin is not only associated with a reduced risk of developing microvascular complications, but also with a significant reduction in cardiovascular morbidity and mortality.[71] This does require the administration of an adequate dose. Up till now metformin was the only blood glucose lowering drug that has convincingly shown a reduction in mortality.

It is estimated that about 15 to 20% of patients have an intolerance or contraindication to metformin and then the choice is between a sulphonylurea derivative and a TZD. There is little difference between the two drugs with respect to efficacy and weight gain. There are no studies that compare the TZDs and sulphonylurea derivatives with respect to cardiovascular mortality. Based on their mechanism of action and the limited evidence from the PROactive trial, TZDs and more particularly pioglitazone may have some advantage (positive effect on cardiovascular risk factors), whilst theoretically sulphonylurea derivatives can be disadvantageous (inhibition of cardioprotective mechanisms). However, tens of years of experience with sulphonylurea derivatives, their rapid onset of action, their favourable side effect profile and the lower costs are arguments in favour of sulphonylurea derivatives. In the future, the oral blood glucose lowering drugs may present themselves on the basis of their protective effect on β-cell function of the pancreas. Such an effect can be translated into a postponement of secondary failure.

Combination therapy

When a patient fails on monotherapy with sulphonylurea derivatives and there is an intolerance or a contraindication to metformin, then a TZD is the most obvious next step. The TZDs were originally approved for this indication. When a patient fails on monotherapy with metformin, a sulphonylurea derivative or a TZD can be prescribed. The arguments to choose a sulphonylurea derivative or a TZD are in fact similar to the situation of metformin intolerance (see previous paragraph). Because type 2 diabetes mellitus is a chronic and progressive disorder, an extra step in pharmacotherapy will be necessary every three to four years, and therefore the majority of patients will ultimately use a combination of drugs.[72]

Combination of three drugs

After some years, many patients will also fail on combination therapy, which in Europe will mainly consist of the combination of metformin with a sulphonylurea derivative. According to most guidelines, patients should then be treated with insulin therapy with continuation of metformin (and even also a sulphonylurea derivative). Theoretically, a TZD could also be added to the combination of metformin and sulphonylurea derivative (triple therapy). A number of studies have shown that triple oral therapy is effective,[20] and approximately as effective as addition of insulin, but not more cost-effective.[73-75]

Combination of TZDs with insulin

Because the combination of TZDs and insulin is associated with an increased risk for development of fluid retention and congestive heart failure, the combination is currently contraindicated in Europe. TZDs do improve glycaemic control in insulin-treated patients[76,77] although often at the expense of substantial weight gain. Use of the combination treatment (TZDs + insulin) thus appears limited and should be restricted to physicians experienced in diabetes treatment.

NOTE

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REVIEW

Antiviral treatment for chronic hepatitis B virus infection – immune modulation or viral suppression?

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ABSTRACT

The availability of nucleoside analogues has broadened treatment options for chronic hepatitis B virus (HBV) infection. Registered treatment for chronic hepatitis B currently consists of (pegylated) interferon, lamivudine and adefovir, while entecavir is expected to be licensed in the short term. Treatment is generally recommended for patients with high serum HBV DNA and elevated ALAT, indicating the host's immune response against HBV. Induction of an HBV-specific immune response seems crucial for persistent control of HBV infection. Currently available treatment strategies can be differentiated into those that provide sustained off-treatment response and those that provide therapy maintained response. A finite treatment course with immunomodulatory agents (interferon-based therapy) results in sustained response in about one third of patients, while nucleoside analogue treatment generally requires indefinite therapy without a clear stopping point. Since nucleoside analogues are well tolerated, prolonged therapy is feasible, but a major drawback is the considerable risk of developing antiviral resistance, which occurs most frequently in lamivudine-treated patients and to a lesser extent during adefovir or entecavir therapy. In our opinion, treatment with peginterferon should therefore be considered first-line therapy in eligible patients with a high likelihood of response based on serum HBV DNA, ALAT and HBV genotype. Patients not responding to PEG-IFN therapy or not eligible for peginterferon therapy should be treated with nucleos(t)ide analogues.

KEYWORDS

Adefovir, interferon, lamivudine, nucleoside analogues, peginterferon

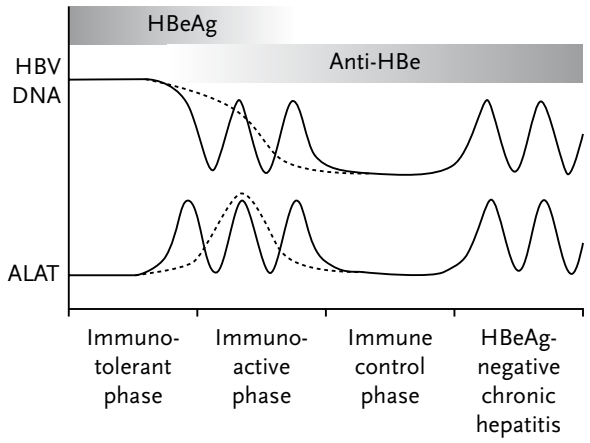
INTRODUCTION

Worldwide more than two billion people have been infected with hepatitis B virus (HBV) and chronic HBV infection affects about 400 million people.[1,2] It is estimated that more than 500,000 people die annually due to HBV-associated liver disease, largely because of cirrhosis and/or hepatocellular carcinoma.[3] Despite the availability of safe and effective vaccines for more than two decades, HBV infection is still a global health problem. The approach to the treatment of chronic HBV infection has dramatically changed over the past decade and the current availability of a number of antiviral drugs adds to the complexity of management of chronic HBV. This paper provides a practical review of available treatment options to guide decisions on optimal therapy based on both patient and treatment characteristics. The main focus will be on deciding between a finite course of immunomodulatory therapy with (pegylated) interferon (IFN) or prolonged viral suppression with nucleoside analogues.

Natural history

In adults, infection with HBV is usually asymptomatic and results in chronic infection in <5% of patients.[3] Infection at younger age is associated with a higher risk of chronic infection, up to 90% in the setting of perinatal transmission.[3] Patients can present with chronic HBV in one of four phases of infection (*figure 1*).[4] In the immunotolerant phase of infection, hepatitis B surface

Figure 1. *Natural history of chronic hepatitis B infection*



This figure shows the phases in chronic hepatitis B infection. Patients can be categorised in one of these four phases depending on serum HBV DNA and ALAT, and the presence or absence of HBeAg and anti-HBe.

antigen (HBsAg) and hepatitis B e antigen (HBeAg) are present and HBV DNA levels are high, >1.0 x 10^5 copies per millilitre (c/ml). Hepatic inflammation is mild with normal or minimally elevated serum alanine aminotransferase (ALAT) levels and minimal necroinflammation on liver histology. In the immuno-active phase, HBsAg, HBeAg and high HBV DNA are still present, while an active immune response results in hepatic inflammation with elevation of serum ALAT. In the immune-clearance phase HBeAg is present and HBV DNA levels can be high or fluctuating. Liver inflammation is present with elevated serum ALAT and active inflammation on liver histology; loss of HBeAg and seroconversion to anti-HBe can occur. The immune-control phase follows HbeAg seroconversion. In this phase hepatic inflammation is minimal and HBV DNA levels are low due to continuous host immune response. This phase of infection is also referred to as the 'inactive carrier state'. In an increasing number of patients with HBeAg-negative HBV, biochemical and histological activity recur and HBV DNA levels are high, resulting in HBeAg-negative chronic hepatitis. These patients often originate from the Mediterranean basin, and are infected with hepatitis B variants that hamper the production of HBeAg. The most commonly described mutation is a G to A transition at position 1896 of the precore region. Three major patterns of HBeAg-negative HBV can be distinguished: a recurrent form with exacerbations and periods of remission (45%), an unremitting form (36%), and an unremitting form with acute exacerbations (20%).[5]

Despite the occurrence of HBeAg-negative HBV, HbeAg seroconversion is still usually associated with improved long-term outcome and therefore considered an important event in the natural course of chronic HBV.[6] Spontaneous HbeAg seroconversion occurs in 8 to 15% of patients in Western countries.[3] Before achieving HbeAg seroconversion many patients have episodes of acute exacerbation.[7,8] The chance of HbeAg seroconversion during acute exacerbation increases with increasing serum ALAT levels, to 45% in patients with ALAT >5 times the upper limit of normal (ULN).[9,10]

Progression to cirrhosis

The overall annual incidence of progression to cirrhosis in chronic HBV-infected patients is about 6%, with a cumulative five-year probability of 20%.[11] In HBeAg-positive patients the annual incidence of progression to cirrhosis is 2 to 5%.[3] Factors associated with an increased rate of progression to cirrhosis include high serum HBV DNA, coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV), recurrent episodes of acute exacerbation and severe necroinflammation at diagnosis.[3,12-14] The probability of survival five years after diagnosis of cirrhosis is 84%.[15] Hepatic decompensation occurs at an annual rate of about 3% in cirrhotic patients, with a five-year cumulative incidence of 16%.[3] Development of decompensated cirrhosis is associated with survival of only 35% at five years.[16]

Hepatocellular carcinoma

The development of hepatocellular carcinoma (HCC) is a major global health problem.[17] Cirrhosis predisposes to HCC and the majority of patients with HCC have underlying cirrhosis (80 to 90%).[18] The annual incidence of HCC in European patients with chronic hepatitis B is about 2.2% in patients with compensated cirrhosis, with a five-year cumulative incidence of about 10%.[18] In Asians the incidence of HCC is higher with an annual rate of 3.2% in patients with cirrhosis and a five-year cumulative incidence of 15%.[18] Predictors of the occurrence of HCC in cirrhotic patients include older age, male sex, sustained activity of liver disease, high HBV DNA level, HbeAg positivity, coinfection with HCV or HIV and alcohol abuse.[18-21] Screening for HCC, with monitoring of α-fetoprotein levels and six-monthly radiographic examination should be considered for patients at increased risk of developing HCC.[22]

Hepatitis B virus genotypes

Hepatitis B virus has been classified into eight genotypes (A-H) *(table 1)*.[23-25] Genotypes A and D are most frequently observed in Europe and North America, while genotypes B and C are prevalent in Asia. Compared with genotype C, genotype B is associated with spontaneous HBeAg seroconversion at younger age, less active liver disease, a slower rate of progression to cirrhosis and less frequent development of HCC.[26-28] Findings on the relationship of other genotypes with clinical outcome are contradictory.[29,30] HBV genotype has been reported to be associated with

response to (pegylated) interferon treatment. HbeAg seroconversion was found to occur more often in patients with genotype A and B than in those with genotype C and D.[31-33] Genotype B seems to have a better virological response to lamivudine than genotype C.[34]

Hepatitis B virus immunopathogenesis

Hepatitis B virus specific T-cell response plays a crucial role in control of viral infection. A vigorous, polyclonal and multispecific peripheral blood T-cell response can be observed in patients with acute self-limiting HBV.[35,36] Activated HBV-specific helper and cytotoxic T-cells are still present several years after recovery from acute hepatitis B and seem to be maintained by continuous stimulation by minute amounts of persisting virus. Therefore, resolution of disease does not imply complete eradication of infection but merely reflects the capacity of HBV-specific T-cells to persistently control HBV infection.[37,38] Viral persistence is believed to be associated with functional tolerance of helper T-lymphocytes and cytotoxic T-lymphocytes to HBV.[39] In chronic HBV-infected patients levels of HBV-specific helper T-cells and cytotoxic T-lymphocytes are generally very low or undetectable.[35]

MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

Patients eligible for antiviral treatment

Antiviral treatment is, in general, not recommended for patients with acute hepatitis B, since the outcome of acute hepatitis B is good in the vast majority of immunocompetent adult patients. For HBeAg-positive patients, treatment is recommended for chronically infected patients with HBV DNA >10^5 c/ml and persistence of elevated ALAT levels (more than twice the upper limit of normal) over a three to six month period (*table 2*). An HBV DNA level of 10^4 c/ml should be used for HBeAg-

Table 1. *Geographical distribution of hepatitis B virus genotypes*

Genotype	Subtypes	Geographical distribution
A	adw2, ayw1	North-Western Europe, Spain, Poland, USA, Central Africa, India, Brazil
B	adw2, ayw1	Southeast Asia, Taiwan, Japan, Indonesia, China, Hong Kong, Vietnam, Thailand
C	adw2, adrq+, adrq-, ayr	Far East Asia, Taiwan, Japan, Korea, China, Hong Kong, Thailand, Indonesia, Polynesia, Solomon Islands, Vietnam, India, Australia, USA, Brazil
D	ayw2, ayw3	Mediterranean area, Albania, Middle East, Turkey, Iran, India, Spain, Czech, Russia, USA, Brazil, Solomon Islands
E	ayw4	West Africa
F	adw4q-, adw2, ayw4	Central and South America, Bolivia, Venezuela, Argentina, Brazil, Polynesia, Alaska
G	adw2	France, Germany, USA
H	adw4	Central and South America

This table shows the association of eight hepatitis B virus genotypes with various subtypes and geographic distribution according to genotype.

Table 2. *Management strategies in chronic hepatitis B*

Stage of disease	HBeAg status	ALAT	HBV DNA (c/ml)	Management strategy
Compensated liver disease	HBeAg positive	≥2x ULN	≥1.0 x 10^5	Antiviral treatment indicated (PEG-IFN or nucleos(t)ide analogue therapy)
		<2x ULN	≥1.0 x 10^5	3 monthly monitoring, consider liver biopsy (consider treatment in case of active necroinflammation)
		<2x ULN	<1.0 x 10^5	3 monthly monitoring
		≥2x ULN	<1.0 x 10^5	Exclude other causes of hepatitis, consider liver biopsy
	HBeAg negative	≥2x ULN	≥1.0 x 10^4	Antiviral treatment indicated (PEG-IFN or nucleos(t)ide analogue therapy)
		<2x ULN	≥1.0 x 10^4	3-6 monthly monitoring, consider liver biopsy (consider treatment in case of active necroinflammation)
		<2x ULN	<1.0 x 10^4	6-12 monthly monitoring
		≥2x ULN	<1.0 x 10^4	Exclude other causes of hepatitis, consider liver biopsy
Decompensated liver disease	HBeAg positive	Any level	Positive by PCR (>300)	Antiviral treatment indicated (nucleos(t)ide analogue therapy)
	HBeAg negative	Any level	Positive by PCR (>300)	Antiviral treatment indicated (nucleos(t)ide analogue therapy)

This table shows management strategies for chronic hepatitis B infected patients based on the stage of liver disease, HBeAg status, HBV DNA level and serum alanine aminotransferase (ALAT). For patients with no treatment indication at this moment, monitoring of these variables at various intervals is recommended. ULN = upper limit of normal; PCR = polymerase chain reaction.

negative patients, since this level was found to differentiate patients from having HBeAg-negative chronic hepatitis or being inactive carriers.[40] In HBeAg-negative patients with HBV DNA >10^4 or HBeAg-positive patients with HBV DNA >10^5 c/ml, and presence of normal ALAT levels, a liver biopsy may be considered to guide decisions on antiviral therapy.[41] In case of active necroinflammation, antiviral treatment can be considered. In patients with histological or clinical evidence of advanced fibrosis or cirrhosis, treatment with lamivudine has shown to reduce progression to decompensated liver disease and hepatocellular carcinoma.[42] Since serum HBV DNA has become increasingly important in the management of chronic HBV, use of standardised assays for quantification of HBV DNA is essential.

Patients who are currently not candidates for treatment should be monitored, as their condition may run a fluctuating course and treatment may be needed on future examinations (*table 2*). For HBeAg-positive patients with high serum HBV DNA but normal ALAT levels, monitoring ALAT with three monthly intervals is recommended, with more frequent monitoring when ALAT levels become elevated. Testing for liver chemistry should be performed every six to twelve months to account for reactivation of liver disease in HBeAg-negative patients with low serum HBV DNA and normal ALAT levels.[43]

Goals of therapy

Sustained viral suppression is the key to reduce hepatic necroinflammation and progression of liver fibrosis. Since elimination of HBV infection (HbsAg seroconversion) can only be achieved in a small proportion of patients with currently available antiviral agents, permanent suppression of HBV is the primary goal of treatment. Further, seroconversion to anti-HBe should be pursued in HBeAg-positive patients since this is associated with improved outcome.[44,45]

Definition of response to antiviral treatment

Response to antiviral treatment can be defined as sustained off-therapy or therapy-maintained response. Biochemical response is defined as decrease in serum ALAT to within the normal range. A virological response is defined as HBV DNA <10^5 c/ml or HBV DNA negativity by sensitive molecular assays, and loss of HBeAg in previously positive patients.[3] Histological response is best defined as a two-point decrease in necroinflammatory score with no worsening of fibrosis. Complete response is defined as loss of HBsAg with appearance of anti-HBs.

Treatment of chronic hepatitis B

Two major types of antiviral drugs are being used for the treatment of chronic HBV: drugs that directly interfere with virus replication and drugs that modulate the HBV-specific immune response. Nucleoside and nucleotide analogues, such as lamivudine, adefovir and entecavir, directly inhibit reverse transcriptase and thereby impair viral replication. Interferon (IFN) has marked immunomodulatory, but less pronounced direct antiviral effects. Registered treatment for chronic HBV in most countries currently consists of interferon-alpha, lamivudine, adefovir, peginterferon- -2a and entecavir, of which the last two have recently been approved. Approval of entecavir for the treatment of chronic HBV in Europe is expected in the short term. Advantages and limitations of, and response to a one-year course of treatment with these antiviral agents, as well as factors influencing likelihood of response, are shown in *tables 3* and *4*.

IMMUNOMODULATORY DRUGS

Pegylated interferon-a

Interferon-alpha (IFN-a) was licensed for the treatment of chronic hepatitis B in most countries in the early 1990s. Interferons are naturally occurring cytokines with immunomodulatory, antiproliferative and antiviral properties.[46]

In HBeAg-positive patients IFN-a results in loss of HBeAg in 25 to 40% of patients.[44,47-52] The majority of patients have a durable response; reactivation occurs in 10 to 20% of patients.[44,53,54] Standard IFN-a induced responses are less durable in HBeAg-negative chronic HBV, with sustained response in 10 to 47% (average 24%) at 12 months after cessation of therapy.[55-59] Long-term follow-up studies showed better overall survival and lower incidence of hepatic decompensation and HCC in responders to IFN-a therapy.[44,45,54,60]

The addition of a polyethylene glycol (PEG) molecule to IFN significantly prolongs half-life and results in more sustained IFN activity. Two pegylated IFNs have been studied for the treatment of HBV, a large branched 40kDa PEG linked to IFN a-2a (peginterferon -2a) and a small linear 12kDa PEG linked to IFN-2b (peginterferon -2b).[61] Both these interferons were initially investigated for the treatment of chronic hepatitis C infection and have shown similar tolerability and higher rates of sustained viral response compared with conventional IFN.[62,63] Peginterferon-alpha-2a (PEG-IFN a-2a) has recently been registered for the treatment of chronic HBV in Europe and the United States and should be given by subcutaneous injection once weekly for 48 weeks in a dosage of 180 mg in both HBeAg-positive and HBeAg-negative patients. Results of treatment with PEG-IFN during shorter periods are very limited. Peginterferon-alpha-2b (PEG-IFN a-2b) will only be registered in specific east-Asian countries.

In HBeAg-positive patients treatment with PEG-IFN was found superior to conventional IFN, with loss of HBeAg in 35% and seroconversion to anti-HBe in 29 to 32% of patients.[32,64-66] Long-term follow-up of patients treated with PEG-IFN and lamivudine combination therapy showed

Table 3. *Comparison of drugs approved for the treatment of chronic hepatitis B*

			HBeAg positive		HBeAg negative	
			HBeAg seroconversion		HBV DNA negativity	
Treatment	**Advantage**	**Disadvantage**	**EOT**	**EOFU**	**EOT**	**EOFU**
Alpha-interferon	Finite treatment course No drug resistance	Frequent subcutaneous injection Frequent adverse events Contraindicated in advanced cirrhosis High costs	35% (44, 47-51)*	30% (44, 47-51, 53, 65)*	60% (55-59, 119, 120)*	35% (55-59)*
Peginterferon	Finite treatment course Weekly dosage interval No drug resistance	Subcutaneous injection Frequent adverse events Contraindicated in advanced cirrhosis High costs	40% (32, 64-66)*	35% (32, 64-67)*	63% (68)*	19% (68)*
Lamivudine	Oral administration Good tolerability Low costs	Long duration of treatment High incidence of antiviral resistance	19% (74-78)*	12% (67, 83, 84)*	65% (68, 85, 87)*	10% (68, 86)*
Adefovir	Oral administration Low incidence of antiviral resistance	Long duration of treatment Weak antiviral effect Renal toxicity	12% (93)*	NA	51% (95)*	NA
Entecavir	Oral administration Strongest HBV inhibitor Good tolerability Low incidence of antiviral resistance	Long duration of treatment High costs	21% (102)*	NA	90% (103)*	NA

This table shows mean response rates (HBeAg seroconversion for HBeAg-positive patients and undetectable HBV DNA for HBeAg-negative patients) at the end of treatment (EOT) with various antiviral drugs for 48 to 52 weeks and at the end of follow-up (EOFU) (NA = data not available). Response to therapy is less durable in HBeAg-negative patients compared with HBeAg-positive patients. Further, while (PEG-)IFN associated responses are generally durable, relapse occurs in a large proportion of nucleos(t)ide analogue treated patients after discontinuation of therapy. *References.

Table 4. *Predictors of response to antiviral therapy in HBeAg-positive patients*

Treatment	**Decreased likelihood of response**	**Increased likelihood of response**
(Peg)interferon	Baseline ALAT ≤2 x ULN[119] Baseline HBV DNA >10^9 c/ml[64] Genotype C or D[31-33] HIV coinfection[121]	Baseline ALAT >2 x ULN[119] Baseline HBV DNA ≤10^9 c/ml[64] Genotype A or B[31-33]
Nucleoside analogues	Baseline ALAT ≤2 x ULN[81] HAI 0-9[81]	Baseline ALAT >2 x ULN[81] HAI ≥10[81]

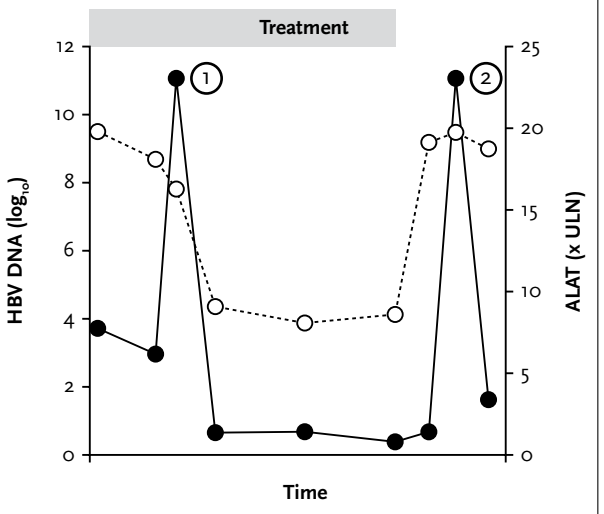
This table shows baseline factors influencing likelihood of response to antiviral therapy in HBeAg-positive patients.
ALAT = alanine aminotransferase; HBV = hepatitis B virus; ULN = upper limit of normal; HAI = histological activity index.

durable response at 72 weeks post-treatment in over 80% of responders.[67] In HBeAg-negative HBV only one large randomised controlled trial using PEG-IFN has been conducted so far.[68] At the end of follow-up, a combined response, with suppression of serum HBV DNA below 10^4 c/ml and normalisation of ALAT, was observed in 36% of patients. HbsAg seroconversion occurs in 3 to 7% of PEG-IFN treated patients, which represents 10 to 20% of virological responders.[32,64,68] HBV genotype appears to predict response to PEG-IFN, with a higher probability of HbeAg loss and HbsAg loss for patients with genotype A (47 and 14%) and B (44 and 9%) compared with genotype C (28% and 3%) and D (25 and 2%).[32,65,69] Addition of a nucleoside analogue to PEG-IFN therapy does not increase response rates in either HBeAg-positive or HBeAg-negative patients, as has earlier been shown in conventional IFN therapy.[32,64,68,70]

Interferon can have several side effects including influenza-like symptoms, fatigue, headache, myalgia, gastrointestinal symptoms (nausea, anorexia, weight loss), alopecia and local reaction at the injection site. These side effects are frequently observed, but rarely lead to discontinuation of treatment. More serious adverse events such as myelosuppression, neuropsychiatric symptoms (irritability, depression and insomnia), neurological symptoms and thyroid dysfunction may require dose reduction or discontinuation.[71,72] Use of PEG-IFN is not recommended in advanced liver disease

since it may potentially precipitate immunological flares and liver failure in these patients (*figure 2*).[73] Adverse events observed during treatment with PEG-IFN are similar to those observed with conventional IFN. The proportion of patients requiring discontinuation of treatment for safety reasons was comparable for PEG-IFN and standard IFN.

Figure 2. *Host and virus induced flares associated with interferon therapy*



This figures shows serum HBV DNA (○) and ALAT (●) levels during and after (peg)interferon (IFN) therapy. IFN potentially induces immunological flares and liver failure: 1. Host-induced flare, with elevation in serum ALAT followed by a decrease in viral load. 2. Virus-induced flare, where serum ALAT elevation is preceded by an increase in serum HBV DNA.[122]

NUCLEOS(T)IDE ANALOGUES

Lamivudine

Lamivudine was the first nucleoside analogue licensed for the treatment of chronic HBV. Lamivudine is a cytosine analogue and inhibits reverse transcriptase by competing for incorporation into growing DNA chains causing chain termination. Lamivudine can be taken orally in a dosage of 100 mg daily, is generally well tolerated and has an excellent safety profile.

HBeAg seroconversion with HBV DNA $<10^5$ c/ml occurs in 16 to 22% of patients by one year compared with 4 to 13% of untreated controls.[74-79] Higher cumulative HBeAg-seroconversion rates were observed with increased duration of lamivudine treatment, with 29% at two years, 40% at three years, and 47% at four years of therapy.[76,79,80] Reduction of serum HBV DNA occurs in 98% of patients.[75] Elevated ALAT >2 x ULN was found to be the best predictor of response to lamivudine.[81] Lamivudine treatment may be discontinued if HBV DNA is suppressed below levels detectable by non-PCR assays and seroconversion from HBeAg to anti-HBe has been achieved. However, lamivudine-induced HBeAg seroconversion is significantly less durable than HBeAg seroconversion following IFN-containing therapies.[82] Data on durability of response to lamivudine are limited, HbeAg seroconversion has been reported to be durable in 50 to 77% of patients.[83,84] Prolonged duration of ongoing lamivudine therapy after HbeAg seroconversion and low pretreatment HBV DNA seem to be associated with decreased relapse rates.[83]

In HBeAg-negative patients serum HBV DNA was undetectable by PCR assay in 68 to 73% of patients after one year of lamivudine therapy. At this time point 73 to 96% of patients showed biochemical response.[68,85,86] However, relapse occurred in 66 to 85% of patients after discontinuation of treatment. In patients treated continuously over one year, response rates progressively declined to about 67% after two years, 60% after three years and 39% after four years.[85,87,88]

Prolonged lamivudine treatment can be used to prevent adverse clinical outcome in patients with advanced liver disease (bridging fibrosis or cirrhosis). Disease progression, defined as a two-point increase in Child-Turcotte-Pugh score, and development of HCC were found to be significantly decreased in lamivudine treated patients compared with untreated controls.[42]

The major drawback of lamivudine, which significantly limits its use as first-line therapy, is the high rate of occurrence of viral resistance. The majority of patients with virological breakthrough show mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the polymerase gene.[88] The most important mutation is a substitution of valine or isoleucine for methionine at position 204 (rtM204V/I).[89] In many patients this is accompanied by a second mutation substituting methionine for leucine in an upstream region (rtL180M). Lamivudine resistance is more likely to occur in patients with high baseline serum HBV DNA levels and patients with HBV DNA $>10^3$ c/ml after six months of treatment.[90] The frequency of resistance increases with the duration of treatment from 24% at one year to 38% at two years, 50% at three years and 67% at four years.[79,80,87] The emergence of lamivudine-resistant mutants is usually associated with an increase in serum HBV DNA and ALAT, and selection of YMDD variants has been associated with worsening of liver histology.[91]

Adefovir dipivoxil

Adefovir dipivoxil is the oral prodrug of adefovir and has activity against both wild-type and lamivudine-resistant HBV.[92] Adefovir is a nucleotide analogue of adenosine monophosphate and acts as a competitive inhibitor and chain terminator of viral replication. Adefovir at the dose of 10 mg daily is well tolerated and has a good safety profile.[93]

In HBeAg-positive patients, serum HBV DNA levels <10^3 c/ml and normalisation of ALAT were observed in 21 and 48% of treated patients, compared with 0 and 16% of untreated controls after one year of adefovir therapy, respectively. HBeAg seroconversion occurred in 12% of patients receiving adefovir compared with 6% in the placebo group.[93] Continued adefovir therapy over one year increased rates of HbeAg seroconversion to 29% after two years and 43% after three years. A similar increase in the proportion of patients with HBV DNA <10^3 c/ml was observed, to 45 and 56% of patients after 96 and 144 weeks, respectively.[94]

In HBeAg-negative patients, treatment with adefovir for one year resulted in serum HBV DNA <10^3 c/ml and normalisation of ALAT in 51 and 72% of treated patients, compared with 0 and 29% of untreated controls.[95] The percentage of HBeAg-negative patients with HBV DNA <10^3 c/ml was 71% at two years and 67% at five years, and ALAT normalised in 73 and 69%, respectively.[96,97] Prolonged adefovir therapy significantly improved liver histology compared with baseline in up to 75 to 80% of patients after five years.[96] Response to adefovir is generally not durable after discontinuation of treatment.[95,97]

Resistance to adefovir is less common and occurs later in the course of HBV treatment compared with lamivudine. To date, mutations in the polymerase gene that have been confirmed to confer resistance to adefovir include rtN236T and rtA181V.[98] The rtN236T mutation occurs most frequently and is associated with the selection of a novel asparagine to threonine substitution at residue rt236 in the domain D of the HBV polymerase.[97] The rtA181V mutation involves a substitution of alanine by valine or threonine at position rt181 of the B domain of the HBV polymerase. The cumulative probability of adefovir resistance is 0 and 28% at one and five years, respectively.[96]

Entecavir

Entecavir is a guanosine analogue and a potent inhibitor of the HBV polymerase. Entecavir has activity against both wild-type and lamivudine resistant HBV. Entecavir can be taken orally, is well tolerated and safe at daily dosages up to 1 mg.[99,100] Entecavir has recently been approved by the FDA for the treatment of chronic hepatitis B and should be given in a dosage of 0.5 mg daily in nucleoside analogue naive patients and 1 mg in lamivudine-refractory patients.[100,101]

In both HBeAg-positive and HBeAg-negative naive patients, one year of entecavir (0.5 mg daily) was found to be superior to lamivudine therapy in reducing serum HBV DNA (6.9 *vs* 5.4 log for HBeAg-positive and 5.0 *vs* 4.5 log for HBeAg-negative patients, respectively) and histological improvement.[102,103] HbeAg seroconversion, HBV DNA negativity by PCR assay and normalisation of ALAT were observed in 21, 67 and 68% of HBeAg-positive patients treated with entecavir for 48 weeks, respectively.[102] Prolonging entecavir therapy to 96 weeks resulted in HBeAg seroconversion in 31% and HBV DNA <10^2 c/ml in 80% of patients, respectively.[104] In HBeAg-negative patients HBV DNA negativity by PCR assay occurred in 90% of patients, while 78% of patients had normalisation of ALAT at week 48.[103] In lamivudine-refractory patients treatment with entecavir 1 mg daily was superior to 0.5 mg daily, and resulted in HbeAg seroconversion in 4%, HBV DNA <10^2 c/ml in 26% and normalisation of ALAT in 68% of patients, respectively.[101] Based on these results, entecavir appears to be a stronger inhibitor of HBV than either lamivudine or adefovir.

Entecavir resistance requires pre-existing lamivudine resistance and additional changes at residue rtT184, rtS202 or rtM250 of the HBV reverse transcriptase.[105] Resistance to entecavir was not observed in nucleoside analogue naive patients treated with entecavir for 48 weeks or 96 weeks.[106-108] In lamivudine-refractory HBV resistance to entecavir has not been described after one year of therapy. However, changes at the rtT184 and/or rtS202 residue were observed in 10% of patients after two years of entecavir treatment.[109]

NEW DRUGS

Emtricitabine is structurally similar to lamivudine (3TC) and has potent antiviral activity against HBV and human immunodeficiency virus (HIV). Seroconversion from HBeAg to anti-HBe can be observed in 12 to 23% of patients after 48 weeks, increasing to 33% after 96 weeks of treatment.[104,110] In HBeAg-negative patients serum HBV DNA was <10^4 c/ml in 76 and 71% of patients after 48 weeks and 96 weeks of treatment, respectively.[104] Mutations associated with resistance to emtricitabine were observed in 12 and 18% of patients after 48 weeks and 96 weeks of treatment, respectively.[104] With the advent of newer antiviral agents with significantly lower risk of antiviral resistance, emtricitabine will possibly have a minor role as monotherapy for HBV.

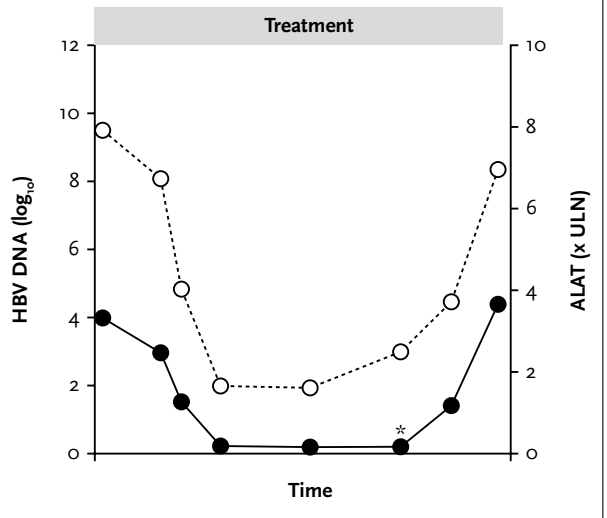
Telbivudine is an L-nucleoside analogue, which is more potent than lamivudine in suppressing HBV DNA.[111] Serum HBV DNA was undetectable by PCR assay in 61% of patients at week 52, while HbeAg seroconversion occurred in 31% of patients. Combination of telbivudine with lamivudine did not result in increased response rates. Resistance to telbivudine emerged in 5% of patients after one year of therapy. Ongoing phase III trials will help determine the role of telbivudine in the treatment of chronic HBV.

Tenofovir disoproxil fumarate is an acyclic nucleotide analogue and has been approved for the treatment of HIV infection. Dosage of tenofovir for hepatitis B infection is 300 mg daily. Tenofovir seems more potent in suppression of HBV DNA than adefovir, with HBV DNA undetectable by PCR assay in all patients treated with tenofovir compared with 44% of patients treated with adefovir at week 48.[112] Currently, randomised controlled trials comparing tenofovir and adefovir are being performed.

ANTIVIRAL RESISTANCE

The highest incidence antiviral resistance has been reported during lamivudine treatment,[80] while resistance to adefovir and entecavir is less common.[96,105] During nucleoside analogue treatment, close monitoring for antiviral resistance is advised, since hepatitis flares have been reported following lamivudine resistance. Antiviral resistance should be suspected if rebound of viral replication (1 $\log_{10}$ increase in serum HBV DNA) occurs in a fully compliant patient after initial response, antiviral resistance testing should then be considered (*figure 3*). It is still being debated whether combination nucleoside analogue treatment should be given, as for HIV infection, or subsequent introduction in case of nonresponse or resistance should be used. Prolonged combination therapy after emergence of antiviral resistance does not seem beneficial.[113] However, whether a shorter overlap period of combination therapy is preferable in patients with advanced liver disease before discontinuing initial treatment has not been assessed. Sequential monotherapy may facilitate resistance to other drugs and may ultimately lead to multiresistance.[109] Following that rationale, lamivudine treatment may negatively influence future treatment options due to the high incidence of antiviral resistance. Furthermore, a recent study showed decreased responsiveness of lamivudine-resistant patients to a course of PEG-IFN.[114] Using lamivudine as initial therapy is therefore highly questionable. Currently adefovir is preferable as first-line nucleoside analogue therapy because of its favourable resistance profile. Entecavir and tenofovir seem to be the drugs with most potent anti-HBV activity and lowest rate of antiviral resistance discovered to date and may become the new standard in nucleos(t)ide analogue treatment for chronic hepatitis B.

Figure 3. *Selection of a mutant HBV associated with antiviral resistance*



This figure shows the emergence of hepatitis B virus variants associated with antiviral resistance during nucleos(t)ide analogue treatment. Antiviral resistance should be suspected if a 1$\log_{10}$ increase in serum HBV DNA (○) is observed (*), this generally precedes rise in ALAT (●) and detectability of resistant hepatitis B variants.

VIRAL SUPPRESSION OR IMMUNE MODULATION?

The approach to treatment of hepatitis B has rapidly changed over the past decade. The treatment landscape has advanced with the availability of multiple new antiviral agents. However, despite this major progress, long-term off-treatment control has not been achieved in a large proportion of patients. Worldwide, evidence-based treatment guidelines for the management of chronic hepatitis B have been developed.[3,22,115] These documents make few specific recommendations as to whether pegylated interferon or nucleoside analogues should be used as first-line therapy. Because both approaches have proven effective, but also have advantages and limitations, the question arises what treatment regime should be used as first-line therapy. The major difference between these treatment strategies is providing sustained off-treatment response with a finite treatment course (IFN) *vs* therapy-maintained response (nucleoside analogues).

Of currently available antiviral agents, peginterferon-based therapies result in the highest probability of sustained off-treatment response. On the other hand, treatment with nucleoside analogues over prolonged periods is feasible and viral and biochemical response can generally be maintained. Since response to these agents is generally not durable after discontinuation of therapy, it is currently proposed that nucleoside analogue therapy needs to be continued indefinitely. This subsequently imposes a considerable risk for antiviral resistance. In our opinion, these findings provide a strong argument in favour of immunomodulatory therapy as first-line treatment for chronic hepatitis B.

Irrespective of the type of antiviral therapy used, sustained virological response results in improved biochemical, histological and clinical outcome. The main goal of antiviral therapy in chronic hepatitis B therefore remains achieving sustained viral suppression, preferably with a finite course of therapy. Individual patient characteristics such as age, comorbid disorders and likelihood to tolerate potential side effects should also be included in deciding on the optimal treatment regime.

Since PEG-IFN results in the highest rates of off-treatment response, treatment with this drug should be considered as first-line therapy in eligible patients with a high likelihood of response. This includes HBeAg-positive patients with genotype A or B, serum ALAT more than twice the upper limit of normal

and moderate HBV DNA levels (10^5 to 10^8 c/ml). Although data on PEG-IFN in HBeAg-negative chronic HBV are limited, PEG-IFN therapy may also be preferential in these patients. For patients with a low likelihood of response to or not eligible for PEG-IFN therapy, patients not tolerating PEG-IFN therapy, or with persistent hepatic inflammation and high viral load after a one-year course of PEG-IFN, treatment with nucleoside analogues should be considered. For several patient groups nucleoside analogues are the antiviral drug of choice. This includes patients with advanced cirrhosis, patients starting chemotherapy,[116] immunocompromised patients,[117] and pregnant patients with very high HBV DNA levels (>10^9 c/ml).[118]

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ORIGINAL ARTICLE

Diagnostic errors; the need to have autopsies

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ABSTRACT

Introduction: In geriatric patients, atypical presentation and limitations in diagnostic scope may lead to underdiagnosis. The aim of this study was to establish the frequency, nature and causes of clinical diagnostic errors in a geriatric population.
Design: A retrospective study.
Methods: We assessed the accuracy of clinical diagnosis using autopsy results as our gold standard. Factors likely to influence accuracy of clinical diagnosis were identified. We used the (modified) classification of Goldman *et al.* to define discrepancy.
Results: We analysed 93 autopsies of a total of 331 deaths (28%). Discrepancies in major diagnoses were seen in 36 cases (39%). In 17 of these, clinical management might have been different if the diagnosis had been made premortem. These were: pulmonary embolism (4); unrecognised infection (4); intestinal ischaemia (3); ruptured aortic aneurysm (2); malignancy (1); tracheal obstruction (1); intestinal obstruction (1) and acute pancreatitis (1). Discrepancies in minor diagnoses were seen in 46 cases (50%). About one third of these were clinically relevant. Discrepancies occurred more frequently if there was a degree of uncertainty about clinical diagnosis (p<0.001).
Conclusion: Major discrepancies between clinical diagnosis and autopsy findings were seen in 39% of our study population. They occur more often in the case of uncertain clinical diagnosis. Our findings stress the continuing and important role of autopsy in improving clinical practice in geriatric medicine.

KEYWORDS

Autopsies, diagnostic errors, geriatric medicine

INTRODUCTION

When it comes to diagnostic accuracy, autopsy is – and probably will remain for some time to come – the gold standard. Autopsy has been in use as a diagnostic tool for more than 3000 years. The Sumerians used animal entrails for divination of the future. The ancient Greeks used autopsy for the study of human anatomy. Galen made the link between visible pathology and disease. But it was not until the Renaissance in Europe that autopsy became standard practice. The famous Dutch physician Herman Boerhaave established the link between clinical syndromes and postmortem findings.[1] After the heyday of autopsy in the 19th and early 20th centuries, the technique has seen a steady decline in popularity. Nowadays, autopsy rates of 5% are no exception.[2]
Yet autopsy remains a valuable tool to evaluate the diagnostic and therapeutic process. Especially in the geriatric population because both the atypical presentation of disease and limitations in diagnostic scope may lead to underdiagnosis of potentially treatable disorders. The aim of this study was to establish the prevalence of diagnostic error in a geriatric population, using autopsy findings as our gold standard. Furthermore, we identified factors, both general and specifically geriatric, which were likely to negatively influence clinical diagnostic accuracy.

MATERIALS AND METHODS

Setting

The study was conducted in the Department of Geriatric Medicine of the University Medical Centre Utrecht, a large university-affiliated teaching hospital. The ward admits patients for both acute geriatric medicine and geriatric rehabilitation.

Selection of cases

From the hospital records, we identified all patients who had died while admitted to the geriatric ward of the

University Medical Centre Utrecht and on whom autopsy was performed between 1 July 1992 and 31 December 2002. Only those who died of natural causes were included.

Method

The clinical notes and autopsy reports were reviewed independently by the same reviewer (CMA). From the clinical notes, data were identified on age, gender, length of admission, extent of diagnostic or therapeutic intervention, major and minor diagnoses, level of certainty of diagnosis and whether or not death was expected. From the final autopsy reports, we identified major and minor diagnoses, extent of autopsy and clinical questions asked by the attending physician

Both clinical and autopsy diagnoses were classified according to ICD 10 (International Classification of Disease, tenth edition). Diagnoses were grouped into seven categories: cardiovascular disease, pulmonary disease, neoplastic disease, gastrointestinal disease, systemic infection, renal disease and miscellaneous (remaining diagnoses).

Discrepancies were classified according to the method of Goldman *et al.*,[3] modified by Battle *et al.*[4] (*table 1*). Class 1 errors were defined as discrepant major diagnoses, the knowledge of which antemortem might have led to changes in clinical management and to prolonged survival. Class 2 errors were discrepant major diagnoses, the knowledge and treatment of which would not have prolonged survival. Class 3 errors were discrepant minor diagnoses that would have been treated if known and class 4 errors were discrepant minor diagnoses of possible epidemiological or statistical importance. The remainder were classified as nondiscrepant (class 5) or nonconclusive (class 6). If more than one error occurred in the same case, it was classified according to the worst one.

Assessment

The chief investigator (CMA) identified all discrepancies between clinical and autopsy findings. Those discrepancies were reviewed by all three investigators, who classified them individually and independently. Consensus was sought between the three investigators.

Statistics

To establish correlations and statistical significance, we used Pearson's χ^2 test and Student's T test. All calculations were made using SPSS 10.0.5 statistical software.

RESULTS

In the period under study, 331 people died and 94 autopsies were performed (autopsy rate 28.4%). One of these was a coroner's autopsy and this was excluded from analysis. Therefore, 93 autopsies were used in our analysis. In this population, there were 45 males and 48 females. The average age at death was 81.6 (60 to 102) years. There were 12 full autopsies (both body and skull), 80 body only and one skull only. In 74 cases, there was a completed clinical request for autopsy, including clinical questions to be answered by the pathologist. In 72 cases, all clinical questions could be answered by the pathologist.

According to the classification presented in *table 1*, there were 17 (18.3%) class 1 errors; 19 (20.4%) class 2 errors; 7 (7.5%) class 3 errors and 15 (16.1%) class 4 errors. Thirty-one cases (33.3%) were nondiscrepant and in four cases (4.3%), neither the clinician, nor the pathologist could identify the probable cause of death. In 24 cases, major and minor errors occurred together, making a total of 46 cases (50.5%) in which minor errors were identified.

Major diagnostic errors occurred significantly more often if there was a degree of uncertainty about diagnosis antemortem ($p<0.001$). Age, gender or length of final admission did not correlate with the occurrence of major diagnostic errors. Neither did the occurrence of sudden death or conscious decisions to limit the scope of diagnostic interventions (*table 2*).

Table 1. *Classification of clinical diagnostic error*[2,3]

Class	Definition	Examples
1	Discrepancy in major diagnosis. Knowledge before death would have led to a different management that could have prolonged survival or cured the patient	Pulmonary embolism treated as pneumonia Tuberculosis diagnosed and treated as malignancy
2	Discrepancy in major diagnosis. Knowledge before death would not have led to longer survival, even with correct treatment	Osteomyelitis as the source of a systemic sepsis in patient dying of multiorgan failure
3	Discrepancy in minor diagnosis not directly related to cause of death, but with symptoms that should have been treated or would have eventually affected prognosis	Carcinoma of the lung in patient dying of a ruptured aneurysm, Peptic ulceration in patient dying of pulmonary embolism
4	Discrepancy in minor diagnosis with possible epidemiological or genetic importance	Goitre Asymptomatic gallstones
5	Nondiscrepant diagnosis	
6	No satisfactory diagnosis was found clinically or on autopsy to explain death	Patient died suddenly without clear indication of underlying disease. Autopsy did not elucidate cause of death

Each case is classified only once according to the worst occurring diagnostic error.

The autopsy diagnoses of the class 1 errors were as follows: pulmonary embolism (4); unrecognised infection (4); intestinal ischaemia (3); ruptured aortic aneurysm (2); malignancy (1); tracheal obstruction (1); intestinal obstruction (1) and acute pancreatitis (1).
Clinical diagnostic accuracy was highest for pneumonia (77.8%) and neoplastic disease (63.6%) and lowest for pulmonary embolism (16.7%) (*table 3*).

DISCUSSION

Our main finding was that major diagnostic errors occur in 39% of our population. Of these 17 were class 1 errors, the knowledge of which antemortem would or could have led to a different management and possibly improved survival. The other 19 are class 2 errors, the knowledge and correct treatment of which antemortem would not have improved survival. This illustrates the ongoing importance of autopsy as an instrument of feedback on the clinical diagnostic and therapeutic process in geriatric medicine. Our percentage of diagnostic errors compares quite unfavourably with several other studies.[3,5] In a major review on this subject, Shojania *et al.*[6] found a median major error rate of 23.5% (range 4.1 to 49.8%) and a median class 1 error rate of 9% (range 0 to 20.7%).
There are several possible causes for our relatively high error rate. First, the average age at death in our study was 81.9 years, which is considerably higher than the average in other large studies. Very little is known in the literature about the prevalence of diagnostic errors in the geriatric population as compared with the general population.[7-9]
Increasing age was found to negatively influence diagnostic accuracy in the study by Battle *et al.*,[4] but not in ours. It is likely that this can be explained by the relative homogeneity of our population. With one exception, all our cases would fall within the highest age bracket of their study (65 years and older).
In our opinion, an atypical disease presentation and conscious decisions not to pursue possible lines of diagnostic investigation both contribute to the high percentage of major diagnostic errors. Atypical presentation is common in the geriatric age group. Diseases and disorders may manifest by a paucity or total absence of classical symptoms and only present with general and atypical signs such as fatigue and anaemia. It is important to realise that conscious restrictions in the scope of investigations in the geriatric population does not stem from ageism or nihilism. Frequently, geriatric clinicians refrain from further investigation at the express request of the patients or their relatives. This is motivated by concerns about the impact of the proposed tests on the patient's immediate well-being and the consequences of the possible findings. If there is no suitable therapy for this particular patient, it may be wise not to investigate the possible presence of the disease. These decisions are made on an individual basis, taking into account factors such as comorbidity and physical performance.
These factors lead to a situation in which we are not treating our geriatric patients by the bright neon light of 21st century medical science, but by the flickering candle of the 19th century. This uncertainty may lead to the adoption of the 19th century's post hoc approach to diagnosis by increasing the number of autopsies in the higher age groups.

Table 2. *Factors influencing major error rate*

	Number of autopsies	Major errors		
		n	%	
Total	*93*	*36*	*(39.8)*	
Sex				
- Male	45	18	(40)	NS
- Female	48	18	(37.5)	NS
Clinical diagnosis				
- Certain	30	1	(2.8)	P<0.001
- Uncertain	63	35	(53.8)	
Sudden death	30	14	(46.7)	NS
Expected death	63	22	(34.9)	NS
Age				
- <80 years	35	15	(41.7)	NS
- >80 years	43	18	(41.9)	NS
Full diagnostic scope	50	18	(36)	NS
Final admission				
- <1 week	18	7	(38.9)	NS
- 1 week-1 month	61	20	(32.8)	NS
- >1 month	24	9	(37.5)	NS

P<0.05 was considered statistically significant. NS = nonsignificant.

Table 3. *Predictive value of clinical diagnosis and accuracy of clinical diagnosis as compared by autopsy diagnosis*

	Total	Confirming clinical major diagnosis	%
Autopsy major diagnosis			
Cardiovascular			
- Myocardial infarction	7	4	57.1
- Congestive heart failure	3	1	33.3
- Other	6	4	66.7
Pulmonary			
- Pneumonia	18	14	77.8
- Pulmonary embolism	6	1	16.7
- Other	2	1	50
Neoplastic disease	22	14	63.6
Gastrointestinal disease	11	5	45.5
Systemic infection	7	3	42.9
Renal disease	1	1	100
Miscellaneous	7	6	85.7
Unknown	3	3	100
Clinical major diagnosis			
Cardiovascular			
- Myocardial infarction	5	4	80
- Congestive heart failure	2	2	100
- Other	4	4	100
Pulmonary			
- Pneumonia	21	15	71.4
- Pulmonary embolism	1	1	100
- Other	4	2	50
Neoplastic disease	23	14	60.9
Gastrointestinal disease	8	5	62.5
Systemic infection	10	4	40
Renal	3	0	0
Miscellaneous	8	6	75
Unknown	4	0	0

The range of class 1 diagnostic errors was found to be quite similar to other studies: pulmonary emboli, infections, intestinal ischaemia, ruptured aortic aneurysm, malignancy, intestinal obstruction and acute pancreatitis were seen in our study. In his study, Goldman[3] also found a high number of unrecognised myocardial infarctions. We found none. This may be due to improved diagnostic options in the past 20 years. Pulmonary embolism is still frequently missed despite improved diagnostic tools. This may be due to a low index of suspicion. Two cases of ruptured aortic aneurysm were missed in our study. It is debatable whether these should be called class 1 errors. We decided to do so, because both diagnosis and treatment (acute surgery) are feasible even at a high age. Contrary to the younger age group, ischaemic intestinal disease has relatively few symptoms (diarrhoea and moderate leucocytosis) and may be easily missed or mistaken for other disease. The absence of typical or classical signs and symptoms in general may lead to uncertainty in diagnosis. Fever is often absent in infectious disease in the elderly. Older people frequently have an altered awareness of pain. Major metabolic disturbances such as hyperglycaemia and renal failure present with amazingly mild symptoms. Furthermore, patients with delirium or dementia are less capable of indicating their complaints.

Diagnostic errors go both ways. As *table 3* illustrates, major disease groups are both overdiagnosed and underdiagnosed. When interpreting the results of this table, it is important to keep in mind that for the purposes of this study, only one major diagnosis, both clinical and on autopsy, was allowed. It is very possible that a patient who was clinically classified as having died of cancer was found on autopsy to have died of an acute myocardial infarction, although the cancer was also confirmed. Findings that were felt not to have immediately led to the decease of the patient were classified as minor findings. It happened only very rarely that a major clinical diagnosis was not confirmed either as a major or as a minor autopsy diagnosis.

Minor diagnostic errors were seen in approximately half of all our cases (49.5%). Sonderegger[5] found a rate of 46%.

However, this cannot be compared because we found that minor errors frequently occurred together with major errors and both were counted. The sum total of class 3 and class 4 errors in our study was 23.6%.

Frequent unsuspected minor autopsy findings were scars from old myocardial infarctions, diverticular disease of the colon, generalised arteriosclerosis evidence of previous tuberculosis, renal cysts and thyroid nodules.

There are several limitations to our study. First, its retrospective design. Second, the low percentage of autopsy and finally, the fact that it is limited to patients admitted to one geriatric ward. It would be interesting to compare our findings to those of a similarly aged population of a general medical ward.

Further research in this interesting topic is necessary. A prospectively designed multicentre study with involvement of both geriatric and general medical wards may show whether our findings are typical for either the age group or for the geriatric population.

In conclusion, our findings stress the continuing and important role of autopsy in improving clinical practise in geriatric medicine.

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ORIGINAL ARTICLE

Helicobacter pylori antibiotic resistance in a Dutch region: trends over time

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ABSTRACT

Aim: Most patients treated for *H. pylori* infection receive empirical therapy based on epidemiological data of antibiotic resistance. However, previous European studies indicate that resistance patterns may be changing. Therefore, the aim of this study was to investigate the prevalence of primary clarithromycin and/or metronidazole-resistant *H. pylori* strains over a six-year period (1997-2002) in a regional hospital.

Methods: All patients visiting Slingeland Hospital in Doetinchem, the Netherlands between 1997 and 2002 with a positive *H. pylori* culture were included in this study. Susceptibility to metronidazole and clarithromycin was determined by disk diffusion.

Results: Of the 1355 patients with an *H. pylori* positive culture, 1127 did not have a history of *H. pylori* eradication, 58 did, and for 170 this information was not available. Mean rates of primary resistance to metronidazole and clarithromycin were 14.4% (162/1125) and 1.0% (11/1123), respectively. Primary metronidazole resistance was stable throughout the study period and primary clarithromycin resistance showed a decreasing trend. Patients of foreign descent and from secondary care had a higher chance of harbouring primary metronidazole-resistant *H. pylori* (adjusted OR (95% CI) 1.75 (1.1 to 2.8), and 1.60 (1.1 to 2.2), respectively). Patients with failed *H. pylori* eradication had a higher chance of harbouring metronidazole-resistant *H. pylori* (43 *vs* 14%, p<0.0001) and clarithromycin-resistant *H. pylori* (5.3 *vs* 1.0%, p=0.004) than untreated patients.

Conclusion: Primary metronidazole resistance is stable at a low level, while primary clarithromycin resistance is virtually absent in the eastern part of the Netherlands. Therefore, triple therapy with a proton pump inhibitor, clarithromycin and amoxicillin can remain the empirical treatment of choice in the Netherlands.

KEYWORDS

Antibiotic resistance, clarithromycin, *Helicobacter pylori*, metronidazole

INTRODUCTION

During the past decade it has been established that not only patients with peptic ulcer disease but also a subgroup of patients with functional dyspepsia benefit from *Helicobacter pylori* eradication.[1,2] Therefore, *H. pylori* test-and-eradication has been incorporated in most guidelines for treatment of primary care patients with dyspeptic symptoms.[3-5] As a result, many patients now receive therapy for *H. pylori* infection.

Several therapy regimens are effective for treatment of this infection, but the current European guidelines as well as the Dutch guidelines recommend triple therapy based on a proton pump inhibitor or ranitidine bismuth citrate, combined with two antibiotics (clarithromycin and amoxicillin or metronidazole) as first-line treatment.[3-5] These regimens reach high cure rates in clinical trials.[6] However, cure rates are substantially lower in case of resistance to the antibiotics used.[7-9]

H. pylori can be (or become) resistant to clarithromycin and metronidazole and ideally therapy should be based on culture results. However, with the new noninvasive management strategies, fewer patients have upper gastrointestinal endoscopy.[10] Even if endoscopy is performed, taking biopsies for culture is often omitted because of the high cost. Therefore culture-based antimicrobial susceptibility data are not generally available in routine clinical practice. Thus, the choice of therapy is usually based on epidemiological data of the local prevalence of antibiotic-resistant *H. pylori* strains.

However, the prevalence of antibiotic-resistant *H. pylori* strains may be changing. Van der Wouden *et al.*[11] reported a rapid increase in metronidazole resistance in the northern part of the Netherlands. And several studies in other countries also showed increasing rates of both metronidazole and clarithromycin resistance.[12-15] Therefore, in order to be able to decide which combination of antibiotics should be used for the treatment of *H. pylori* infection recent data on the local antibiotic resistance patterns are needed. Unfortunately there is only one recent Dutch study on this subject. This study by Loffeld *et al.*[16] showed fairly stable rates of antibiotic resistance. But more research is necessary to confirm this for other parts of the Netherlands.
Therefore, the aim of this study was to evaluate the prevalence of both primary and secondary clarithromycin and/or metronidazole resistant *H. pylori* strains in the eastern part of the Netherlands and to monitor changes over a six-year period (1997-2002).

METHODS

Study population

All patients who underwent diagnostic upper gastrointestinal endoscopy in Slingeland Hospital in Doetinchem, the Netherlands, between 1 January 1997 and 31 December 2002, and who had a culture positive for *H. pylori* were included in this study. Data regarding antibiotic susceptibility, gender, age, country of origin, referring physician (primary or secondary care), and previous (failed) *H. pylori* eradication were entered into a database.

H. pylori culture and antibiotic susceptibility testing

H. pylori was cultured from one gastric biopsy specimen (antrum or corpus) on chocolate agar and a Skirrow plate (Regional Laboratory Arnhem, the Netherlands). Plates were incubated in a micro-aerobic atmosphere at 37°C and examined after three, seven ands ten days of incubation. *H. pylori* was identified by colony appearance, Gram staining and positive biochemical tests (catalase, oxidase and urease).

Susceptibility to metronidazole and clarithromycin was determined by disk diffusion: a 16 μg metronidazole disk and a 30 μg clarithromycin disk were placed on separate chocolate agar plates with three to five suspected colonies of *H. pylori*. Plates were incubated in a microaerophilic atmosphere at 37°C for 72 hours. Antibiotic susceptibility was determined by measuring the growth inhibition zone around the disk. Strains were considered resistant to clarithromycin when the growth inhibition zone was <19 mm and to metronidazole when it was <23 mm.[17]

Data analysis

Primary outcome was the prevalence of resistance to metronidazole or clarithromycin. Baseline characteristics of patients harbouring antibiotic resistant and susceptible strains were compared using the χ^2 test. Baseline characteristics and study year were related to the presence of antibiotic resistance using unadjusted and adjusted logistic regression analyses. Data were analysed using SAS software (SAS Institute Inc., USA). Statistical significance was defined as a p value <0.05. Missing values were excluded from analyses.

RESULTS

Population

During the study period 1355 patients had a culture positive for *H. pylori*. Fifty-eight of these patients had had a previously failed attempt to eradicate *H. pylori*, for 170 there were no data available regarding prior *H. pylori*

Table 1. *Baseline characteristics in relation to primary metronidazole resistance and primary clarithromycin resistance*

	Metronidazole		Clarithromycin	
	Susceptible % (n) n=963	Resistant % (n) n=162	Susceptible % (n) n=1112	Resistant % (n) n=11
Gender				
- Male	54 (520)	49 (79)	53 (594)	36 (4)
- Female	46 (442)	51 (83)	47 (517)	64 (7)
Age in years: mean (SD)	55 (16)	56 (17)	55 (16)	60 (20)
Descent				
- Dutch	86 (822)	80 (130)	85 (939)	91 (10)
- Foreign	14 (135)	20 (32)	15 (167)	9 (1)
Referring physician*				
Primary	64 (602)	52 (82)	62 (676)	50 (5)
Secondary	36 (345)	48 (76)	38 (417)	50 (5)

*P<0.05 for the difference between metronidazole susceptible and resistant strains.

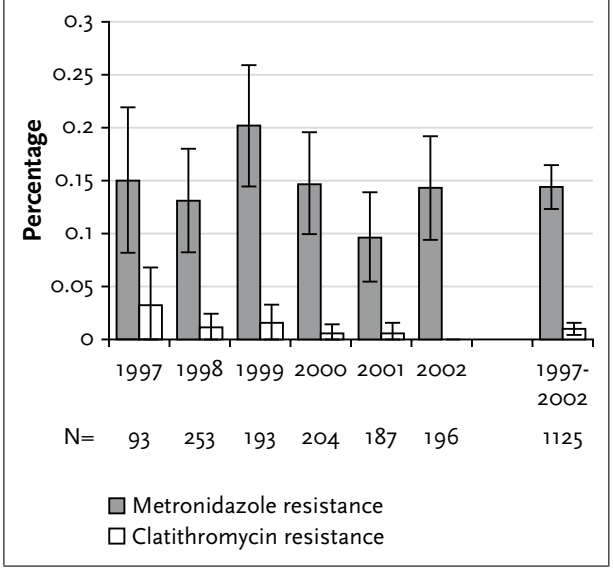
eradication. The remaining 1127 patients who did not have a history of *H. pylori* eradication were studied for primary metronidazole and clarithromycin resistance. *Table 1* shows the baseline characteristics of these patients related to the presence of primary metronidazole and clarithromycin resistance.

Prevalence of antibiotic resistance

Metronidazole susceptibility was successfully tested in 1125 patients and resistance was found in 162 (14.4%, 95% CI 12.3 to 16.5%) of these patients. Clarithromycin susceptibility was successfully tested in 1123 patients and resistance was found in 11 (1.0%, 95% CI 0.4 to 1.6%) of these patients.

Figure 1 shows that the prevalence of metronidazole resistance was fairly stable during the study period (odds ratio for study year 0.96 (95% CI 0.9 to 1.1)). Furthermore, *figure 1* shows that the prevalence of clarithromycin resistance decreased during the study period (odds ratio for study year 0.58 (95% CI 0.40 to 0.9)), although this result is difficult to interpret due to the low number of patients with clarithromycin-resistant strains.

Figure 1. *Proportions of primary metronidazole and clarithromycin resistant H. pylori strains (95% confidence interval)*



Factors associated with primary antibiotic resistance

Table 2 shows that patients of foreign descent and patients referred by a secondary care physician were more likely to harbour metronidazole-resistant strains. It was not feasible to perform these analyses for clarithromycin resistance due to the very low number of clarithromycin-resistant *H. pylori* strains.

Secondary antibiotic resistance

Prevalence of both metronidazole and clarithromycin resistance was higher in the 58 patients with a previous (failed) attempt to eradicate *H. pylori* than in previously untreated patients (metronidazole: 43 *vs* 14% p<0.0001 and clarithromycin: 5.3 *vs* 1.0% p=0.004, respectively).

DISCUSSION

Because most patients are treated for *H. pylori* without prior susceptibility testing it is important to gather epidemiological data on the current prevalence of antibiotic resistance to guide empirical therapy, which was the aim of this study. The present study shows that primary metronidazole resistance was stable throughout the study period (1997 to 2002) with a mean prevalence of 14%. Furthermore, the results show that the prevalence of primary clarithromycin resistance was very low (mean prevalence 1%) and showed a decreasing trend.

Our figures are somewhat lower than those recently reported by Loffeld *et al.*[16] for 976 *H. pylori* positive cultures from another Dutch region (26% primary metronidazole resistance and 5% primary clarithromycin resistance). This can partly be explained by the higher proportion of patients of Mediterranean descent (who have a higher prevalence of antibiotic resistance) in the study by Loffeld *et al.* However, our results are comparable with data from other Dutch regions, published as abstracts only.

Table 2. *Factors associated with primary metronidazole resistance*

Factor	Unadjusted analysis odds ratio (95% CI)	Adjusted analysis odds ratio (95% CI)
Age group (old *vs* young)	1.11 (0.8-1.6)	1.23 (0.8-1.8)
Gender (female *vs* male)	1.24 (0.9-1.7)	1.22 (0.9-1.7)
Descent (foreign *vs* Dutch)	1.50 (1.0-2.2)	1.75 (1.1-2.8)*
Referring physician (secondary *vs* primary care)	1.62 (1.2-2.3)*	1.60 (1.1-2.2)*
Year of the study period	0.96 (0.9-1.1)	0.93 (0.8-1.1)

*P<0.05.

Arents *et al.*[18] studied 6648 *H. pylori* positive cultures in the north of the Netherlands and found that primary metronidazole resistance had decreased from 28% in 1996 to 13% in 2001, and that clarithromycin resistance ranged from 1 to 3% without evident trends. Moreover, Janssen *et al.*[19] found a 14% metronidazole resistance and a 3% clarithromycin resistance when studying 961 *H. pylori* positive cultures in the south of the Netherlands.

Our results do not confirm the rapid increase in metronidazole resistance (from 7% in 1993 to 32% in 1996) as reported by Van der Wouden *et al.*[11] for 1037 isolates from the north of the Netherlands. However, more recent data from that area did not confirm this increase; in fact they showed that this increase turned into a decrease after 1996.[18]

Compared with other European countries both primary metronidazole resistance and primary clarithromycin resistance are low in the Netherlands.[12-14,20,21] These differences in primary antibiotic resistance may be related to the use of antibiotics for other indications. In the Netherlands sales of antibiotics are lower than in any other country of the European Union. In fact, in France, Spain, Italy and Greece sales of macrolide antibiotics are about four times higher than in the Netherlands and this may explain the higher prevalence of clarithromycin resistance in these countries.[22-24]

Our results showed that patients originating from foreign countries (nearly all from Turkey) were more likely to harbour strains resistant to metronidazole than patients of Dutch descent. This has been confirmed by other research[16] and it probably reflects the higher frequency of metronidazole use for other indications in these countries. Furthermore, both metronidazole and clarithromycin resistance were about four times higher in patients with a history of failed *H. pylori* eradication than in untreated patients. This reflects the induction of secondary resistance to metronidazole and/or clarithromycin depending on the antibiotics used in the failed *H. pylori* eradication. Therefore, it is important to take a thorough medical history regarding previous failed *H. pylori* treatments in order to determine which antibiotics can be used for a subsequent attempt to eradicate *H. pylori*.

In this study *H. pylori* susceptibility was tested using disk diffusion. Although agar dilution is considered the gold standard, this method is too demanding for everyday practice and it can be replaced by E-test or disk diffusion. Initially E-test was considered superior to disk diffusion, but several studies show that both methods produce comparable results. In comparison with agar dilution both methods are hampered with some discordant results for metronidazole susceptibility, especially in the intermediate susceptibility range.[25-27]

Based on our results it should be advised to use clarithromycin-based triple therapy rather than metronidazole-based triple therapy for empirical first-line treatment of *H. pylori* infections in our region. Triple therapy with clarithromycin and amoxicillin is the treatment of choice because it is not hampered by metronidazole resistance[28] and because this regimen cannot induce double antibiotic resistance (to both clarithromycin and metronidazole).[29,30] Therefore, failure of this therapy still leaves the option of empirical second-line therapy based on metronidazole, preferably quadruple therapy since this therapy may overcome metronidazole resistance.[9,30] Regarding the low prevalence of primary antibiotic resistance, culture and susceptibility testing are not necessary for this combination of first-line and second-line therapy.

In conclusion, in the eastern part of the Netherlands, primary metronidazole resistance was stable at a low level, while primary clarithromycin resistance was virtually absent. Therefore, triple therapy with clarithromycin and amoxicillin can remain the empirical treatment of choice in this area.

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CASE REPORT

Fatal aspiration of polyethylene glycol solution

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ABSTRACT

Endoscopy of the colon requires adequate cleansing of the entire bowel. Several laxative regimens have been propagated, but bowel preparation with polyethylene glycol (PEG) solution is popular because of the easy application and good cleansing results. Although very safe in daily use, complications of this bowel-cleansing procedure have been reported and aspiration of the PEG solution is a possible and serious hazard. A case report is presented of a patient who aspirated the PEG solution and ultimately died because of respiratory failure.

KEYWORDS

Fatal aspiration, polyethylene glycol, respiratory failure

INTRODUCTION

Endoscopy of the colon is widely applied and indications for this procedure are mostly abdominal symptoms, rectal bleeding, anaemia, diarrhoea or a family history of malignancy or colorectal adenomas. A successful procedure requires total visualisation of the colon and rectum. Therefore, complete bowel preparation is mandatory and several laxatives can be used for this purpose. The ideal bowel-cleansing preparation should be efficient, safe and tolerable for the patient and convenient in daily practice. Polyethylene glycol (PEG) solutions are generally used because they are efficient in cleansing the entire colon and meet the mentioned safety criteria concerning the patient. Although routinely applied without major side effects, unexpected complications can occur. This will be demonstrated in the following case history.

CASE REPORT

An 86-year-old male was admitted because of abdominal pain located in the right side of the abdomen, alterations in stool frequency and consistency, nausea and weight loss. His medical history revealed COPD, spondylarthritis, a stenosis in the left carotid artery and recently a transient neurological deficit. He smoked ten cigarettes a day and did not use alcohol. On physical examination, a slim male was seen (length 182 cm, weight 68 kg) with normal blood pressure, pulse frequency and body temperature. Examination of the abdomen showed normal peristalsis. Laboratory examinations were normal except for a slightly elevated level of creatinine (96 μmol/l; normal 64 to 108 μmol/l), a decreased serum albumin (33.6 g/l; normal 35 to 50 g/l) and a microcytic anaemia (haemoglobin count 7.4 mmol/l; normal 8.7 to 10.7 mmol/l). Ultrasound examination of the abdomen only showed a small aneurysm of the aorta with a diameter of 4 cm and stones in the gallbladder. Chest X-ray (*figure 1*) showed bilateral pulmonary emphysema.

Malignancy in the ascending colon or caecum was suspected because of the microcytic anaemia and the abdominal symptoms. A colonoscopy was scheduled and bowel preparation was started conform the local procedure, consisting of four litres of PEG solution (Klean-Prep®, Norgine Pharma, Amsterdam, the Netherlands) usually administered in four to six hours. A nasogastric tube was used for administration of the solution because the patient was not able to drink this large amount of fluid. The patient complained of nausea after administration of two litres solution in three hours, vomited once and the administration of the PEG solution was immediately stopped. Two hours later, the patient became dyspnoeic with a respiration rate of 25 breaths/min. Physical examination revealed rhales, especially in the right lung. Blood gas analysis showed a combined respiratory and metabolic acidosis with hypoxaemia: pH 7.16; pCO_2 8.3 kPa; pO_2 5.3 kPa; HCO_3 mmol/l 21.4;

Figure 1. *Chest X-ray of the patient on admission, with the pulmonary emphysema clearly visualised*

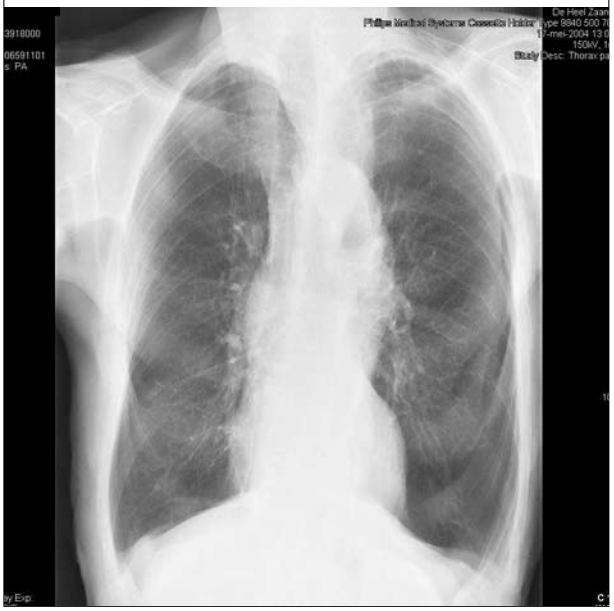
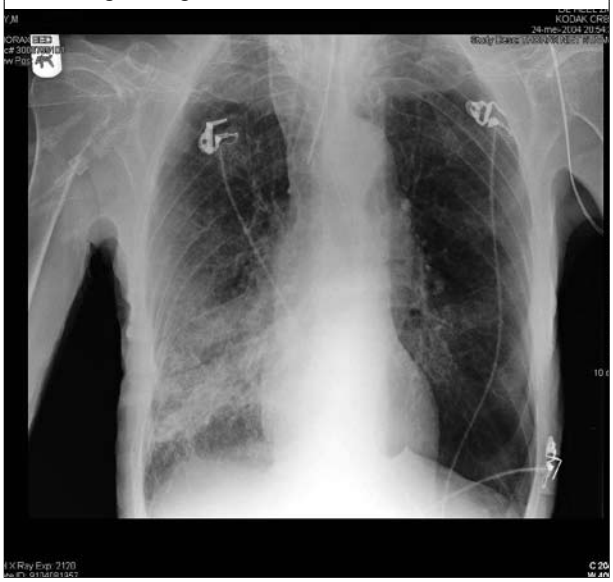


Figure 2. *Chest X-ray before starting the mechanical support, with a massive consolidation clearly visualised in the right lung*



O_2 saturation 61% (normal pH 7.36 to 7.43; pCO_2 35 to 45 mmHg; pO_2 60 to 80 mmHg; HCO_3 22-26 mmol/l; O_2 saturation 95 to 98%).

He was transferred to the intensive care unit, where he was treated with oxygen and antibiotics according local antibiotic practice for aspiration (clindamycin 600 mg and cefuroxim 750 mg, both three times a day). Chest X-ray showed massive consolidation in the right as well as the left lung (*figure 2*). The ongoing worsening of his respiratory function required intubation and respiratory assist. Bronchoscopy with application of NaCl 0.9% was performed to try to remove as much aspirated PEG solution as possible, but did not result in removing the aspirated fluids. During this procedure, diffuse mucosal inflammation and interstitial oedema was seen. Corticosteroids were added to temper the acute respiratory failure; intensive haemodynamic support with norepinephrine, dopamine and enoximone was necessary. Despite maximal supportive care, ongoing acute respiratory distress syndrome developed which resulted in multiorgan failure. Ultimately the patient died; a postmortem examination was not permitted.

DISCUSSION

Because of the good results, PEG-based laxative regimens are increasingly being used in bowel cleansing before endoscopic examination. As can be expected the number of serious adverse events increases accordingly.[1-15]

A fatal case of aspiration of a PEG-based solution is presented here. Five case reports reporting a similar aspiration comprised three children (aged 8, 11 and 8 years)[1,2,4] and three adults (aged 80, 59 and 78 years).[3] All patients were scheduled for colonoscopy and received PEG solution through a nasogastric tube in two to five hours. Aspiration occurred in all patients during or shortly after administration of the solution and support of respiratory functions was necessary shortly after the event. Five patients required transfer to the intensive care unit for mechanical ventilation. Apart from mechanical ventilation, treatment consisted of corticosteroids, antibiotics and diuretics. In one patient, the aspirated PEG solution could be removed successfully. During this procedure diffuse mucosal inflammation and interstitial oedema was seen, which was also the case in our patient.[4] Five patients recovered completely (including all the children), but one patient (a 78-year-old female) died after two weeks because of ongoing adult respiratory stress syndrome.[3]

Disadvantages of PEG are the large amount of fluid needed (up to four litres) and the unpleasant taste. A possible answer is to administer the solution by a nasogastric tube, which is considered an effective and safe method. However, all reported cases of aspiration occurred with the use of a nasogastric tube during administration of PEG solution. Use of prokinetics such as metoclopramide can be considered if the patient experiences nausea while the solution is being given.

Other reported adverse effects for PEG-based lavage solutions are abdominal pain and cramps, vomiting and absorption interactions with simultaneously ingested drugs, but these are inherent to the use of laxatives as a whole. Other more serious adverse events are drug-induced pulmonary oedema, asthma and bronchospasms,[2,6,7,12,15] angio-oedema[8] and pancreatitis.[13]

Aspiration of gastric contents is a serious risk for developing acute respiratory failure or ARDS. Probably one third of the patients who experience gastric aspiration develop acute respiratory syndrome.[16] The reported mortality in this group of patients is high and especially older patients are at risk.[17,18] Predisposing conditions for aspiration are diminished consciousness, dysphagia, neurological disorders and malfunctioning of the physiological mechanisms in the upper gastrointestinal tract that normally prevent aspiration.[19] Possible other mechanisms for aspiration include administration of large amounts of fluid in a short time (which can provoke a gastric spasm) and a recumbent position, which enhances regurgitation and aspiration.

Our patient had no underlying cardiac or neurological disease and only slight renal dysfunction. Severe emphysema was seen on the chest X-ray and is likely to have contributed to the rapid deterioration of his pulmonary function.

Excessive systemic water absorption leading to intravascular fluid overload is a possible cause of pulmonary oedema and has been described earlier after PEG administration.[2,6,7] However, our patient received only two litres of PEG solution and his respiratory condition did not improve after administration of furosemide. Furthermore, his pulmonary condition remained poor during his stay on the ICU as was seen on the repeated chest X-rays, and ventilation and laboratory parameters. This makes respiratory failure caused by intravascular volume overload less likely and points towards a local inflammatory reaction of lung tissue after aspiration of the PEG solution.

Aspirated liquids can theoretically lead to pulmonary oedema / ARDS by affecting the surface tension in the lungs (causing collapse the alveoli and lower bronchial airways) and diffusion of fluids into the alveolar and interstitial space. The performed lavage did not retrieve the aspirated fluid, which implicates that most of the aspirated fluid had already been absorbed in the pulmonary tissues. However, diffuse inflammation and mucosal oedema of the lower airways was seen during endoscopy and this has been reported earlier after aspiration of a PEG solution by Liangthanasarn *et al.*[4] Pneumonitis was also reported in our patient by the radiologist on basis of the repeated chest X-rays.

Therefore, it seems more likely that the PEG itself played a significant role in the acute inflammatory reaction of pulmonary tissue that developed in our patient. A similar hypothesis has been postulated by Paap *et al.*[2] They suggested that PEG solution has hyperosmotic instead of iso-osmotic properties. The solution may then be neutral in gut tissue but thus can lead to intra-luminary fluid shifts in lung tissue after aspiration, causing pulmonary oedema. Besides, it is likely that PEG itself can cause inflammation of pulmonary tissue after aspiration and subsequently a chemical pneumonitis.

It is concluded that, although safe in general, PEG-based solutions administered via a nasogastric tube can lead to aspiration. Administration should be started at a low infusion rate. When well tolerated, the flow can slowly increase to a recommended flow of 20 to 30 ml/minute.[20] During administration vital signs of the patient should be checked regularly. These actions have to be taken in order to prevent complications.

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CASE REPORT

Multiple cysts in the liver autosomal dominant polycystic liver disease

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ABSTRACT

A 45-year-old woman was admitted because of abdominal pain and a feeling of fullness. Ultrasound and CT scan of the abdomen showed a massively enlarged liver with hundreds of cysts and displacement of the right kidney. There were no cysts in the kidneys. Because several members of her family also had multiple cysts in the liver, the diagnosis of autosomal dominant polycystic liver disease (PCLD) was made. Genetic analysis demonstrated a protein kinase C substrate 80 K-H (PRKCSH) gene mutation (1338-2A>G) and confirmed the clinical diagnosis. A brief review of the genetics and possible treatments is given.

KEYWORDS

Autosomal dominant polycystic liver disease, liver cysts, polycystic liver disease

INTRODUCTION

Since the introduction of ultrasound investigation of the abdomen, cysts in the liver and kidney have become normal findings. The majority of diagnosed cysts are small and have no clinical consequences, nor do they cause symptoms. Adult polycystic kidney disease is a well-known disease entity and is characterised by hundreds of cysts in the kidneys and sometimes the liver and accompanying renal failure in most cases. Cysts in the liver may be part of this disease. If multiple cysts are seen solely in the liver, another diagnosis has to be considered. We describe a patient with a grossly enlarged liver due to hundreds of cysts, without involvement of the kidneys.

CASE REPORT

A 45-year-old woman was admitted because of progressive abdominal pain located mainly in the right upper quadrant. She had no relevant medical history and had always been healthy.

Her main complaint was pain in the right abdomen, with a feeling of fullness, her waistband had increased several sizes. She had no complaints of nausea, vomiting or fever. Her urine and stools showed no abnormalities. Her appetite was normal, her weight stable. Physical examination showed a normal body temperature, heart frequency and blood pressure. Heart and lungs showed no abnormalities. The abdomen revealed a very large painful mass in the right upper quadrant extending downwards for more than 10 cm. No signs of chronic liver disease were seen and there was no ascites. Blood tests showed no abnormalities; the transaminases were normal, there was a slight elevation of the alkaline phosphatase (137 U/l) and normal kidney function. Ultrasound examination of the abdomen showed a very large liver with hundreds of cysts varying from 0.7 to 6.5 cm in diameter. CT scan confirmed the ultrasound findings (*figure 1*).

Her family history was positive for the presence of multiple cysts in the liver. Her father had multiple cysts in the liver and one cyst in a kidney without signs of renal failure. Her father's brother underwent surgery because of large cysts in the liver, and her father's sister also had multiple liver cysts. A daughter of this aunt underwent drainage of liver cysts. *Figure 2* shows the family tree.

Genetic analysis was carried out, courtesy of the Department of Gastroenterology of the Radboud University Medical Centre. DNA from a control subject and the patient was amplified with primers surrounding the splice acceptor site of intron 15. Digestion of the wildtype polymerase chain reaction (PCR) product with the restriction enzyme Ban 1 produced fragments of 428 and 175 basepairs (left lane of *figure 3*). Digestion of the mutant 1338-2A>G

Figure 1. *CT scan of the enlarged liver, reaching the pelvi with diffuse cysts with a maximal diameter of 5 cm and displacement of adjacent organs*

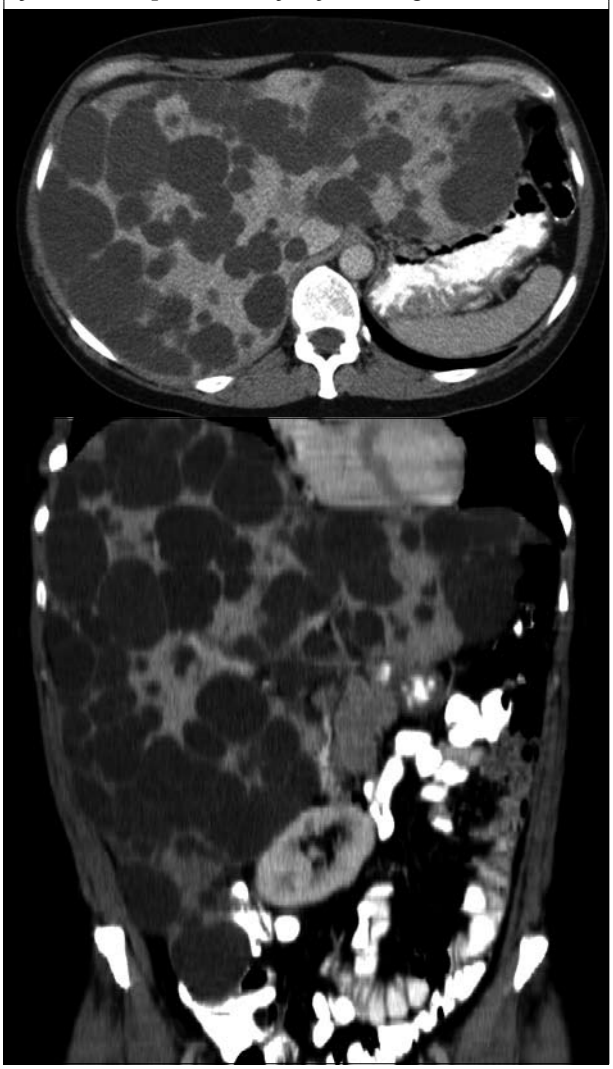
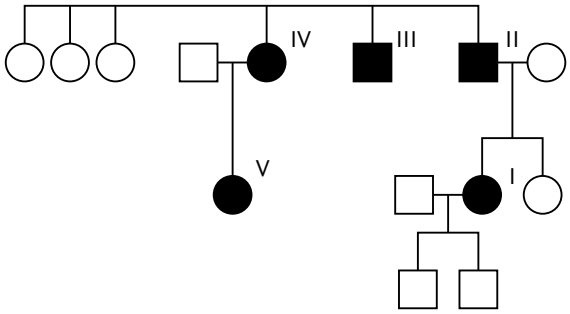
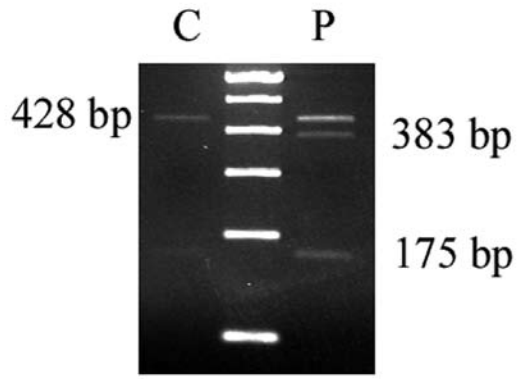


Figure 2. *Family tree*



I: patient; II: father; III: uncle; IV: aunt; V: niece.
○ = female; ● = female with polycystic liver desease;
□ = male; ■ = male with polycystic liver desease.

Figure 3. *Photograph of the gel depicting the genetic analys*



allele resulted in three additional bands at 383, 175, and 45 basepairs (right lane of *figure 3*). This confirms the presence of a 1338-2A>G mutation, hence confirming the clinical diagnosis polycystic liver disease (PCLD).

DISCUSSION

Given the family history and the absence of adult polycystic kidney disease (ADPKD), the diagnosis of polycystic liver disease (PCLD) was made. The diagnosis was confirmed via mutation analysis. PCLD is an autosomal dominant disorder. It usually runs an asymptomatic course. It is seldom diagnosed before puberty and is seen more often and more prominently in women. The cysts in PCLD can increase in size and number during pregnancy or simultaneously with the use of exogenous female steroid hormones.[1] Because of the increased volume of the liver, patients can have symptoms of abdominal distension, abdominal pain and early satiety. Other symptoms are nausea, vomiting, tiredness and shortness of breath.[2,3] Noncystic manifestation of the disease can be mitral valve leaflet abnormalities. True mitral valve prolapse is reported in 8% of patients.[4] Unlike ADPKD, PCLD is not associated with cerebral aneurysms.[4,5] However, in a large series of patients with PCLD one case of death due to subarachnoidal haemorrhage from an aneurysm was noted.[6] In a family with PCLD, two members had an intracranial aneurysm, while in one sibling without liver cysts an aneurysm was detected through screening.[7] Whether the prevalence of cerebral aneurysms is higher than in the general population is a matter of debate. Despite massive cysts, the synthetic capacity of the liver is almost always intact.

Two genes are known to be related to PCLD.[9,10] The first gene is PRKCSH, which encodes for the β-subunit of glucosidase II, an N-linked glycane processing enzyme in the endoplasmatic reticulum. It is located on 19p13.2-p13.1. The second is a SEC63 gene, which encodes a component of the protein translocation machinery in the endoplasmatic reticulum. It is located on 6q21-q23. These findings suggest a role for co-translational protein-processing pathways in maintaining epithelial luminal structure and implicate (noncilial) endoplasmatic reticulum proteins in PCLD. Mutations in these genes can be found in less than one third of the cases. This indicates the presence of at least one more locus associated with this disorder. Clinical genetic testing for PCLD is available and includes genetic sequencing of the coding portion of PRKCSH and/or SEC63.[8,9]

Less than 5% of patients have acute medical complications. These consist of cyst haemorrhage, rupture, infection, uterine prolapse due to displacement, obstructive jaundice, portal hypertension, transudative and exsudative ascites and Budd-Chiari syndrome.[2,3,6,10,11] Treatment should be considered in case of persistent symptoms and complications.

There are no medical therapies for PCLD. Use of somatostatin to block the secretin-induced secretion by hepatic cysts failed to demonstrate any significant effect on hepatic cyst growth size.[12] Cyst aspiration with sclerosis, open or laparoscopic cyst fenestration, combined hepatic resection and fenestration or liver transplantation,[2,3,6,10] are possible treatments. Aspiration combined with ethanol instillation to induce sclerosis of the cyst lining epithelium can be effective. Only small series with variable effect have been described, with variable effect. In the largest series, the symptoms returned after four years in 50% of the cases.[13] Recurrence of symptoms was due to growth of the untreated cysts and not to re-expansion of the treated cysts. This technique is limited by the number and accessibility of the cysts.

Cyst fenestration can be performed, but the peritoneum does not always have the capacity to absorb large amounts of fluids. Morbidity of laparoscopic fenestration was between 33 to 45% and recurrence of symptoms occurred in the majority of cases. Lower recurrence rates were seen in series of large dominant cysts in the anterior segment of the liver. Patients with small cysts throughout the liver have a greater risk of persistence and/or recurrence of symptoms.[6,10] Postoperative morbidity consists of temporary ascites, pleural effusion and rarely biliary leakage.[2] Combined hepatic resection and fenestration is more effective for reducing the hepatic mass and gastric compression. Patients are free of symptoms for a longer period of time than with fenestration alone. Recurrence rates are 0 to 50% and morbidity rates are 38 to 100%. This procedure has an advantage in the case of massive hepatomegaly and severe symptoms of gastric compression.[2] Liver transplantation has been performed in rare cases, especially when the above-mentioned interventions are not an option. One series reported that after a follow-up of 4.4 years, all patients were free of symptoms.[16] Transarterial catheter embolisation (TAE) can be effective.[17] After a follow-up of two years, a decrease in liver volume of 54% was seen. However, this technique can be dangerous; the outcome cannot be accurately predicted and a large area of necrosis can occur. It should be noted that most therapeutic interventions were done in small series and randomised controlled trials are not available.

A careful and thorough examination of the family history led to the final diagnosis of PCLD in this case. Patients should be treated in a specialised centre. Because of the very large liver in this patient she was referred to a centre specialising in both liver surgery and liver transplantation.

ACKNOWLEDGEMENT

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CASE REPORT

Status epilepticus caused by a myxoedema coma

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ABSTRACT

The case of a 63-year-old woman who presented with status epilepticus, coma and hypoventilation is reported. A primary neurological cause was considered. Hypothermia led to further investigations and a diagnosis of severe hypothyroidism. The neurological complications of hyperthyriodism include alteration in mental status with slowness, decreased concentration and lethargy, headache, cranial nerve palsies, dysarthria, hoarseness, myopathy, neuropathy, reflex changes, ataxia, and psychotic episodes. Our patient suffered from a rare consequence of severe hypothyroidism presenting with status epilepticus and she died despite treatment. To our knowledge this is the second patient to be reported with myxoedema coma with this kind of presentation. Despite therapeutic options, there is a high mortality rate.

KEYWORDS

Myxoedema coma, severe hypothyroidism, status epilepticus

INTRODUCTION

Traditionally, status epilepticus is defined as 30 minutes of continuous seizure activity or a series of seizures without return to full consciousness between seizures.[1] In about one third of the cases, an exacerbation of an idiopathic seizure disorder is thought to be the cause. In anther third, the episode of status epilepticus represents the first onset of a seizure disorder. In both conditions the diagnosis is made by exclusion of a myriad of other diseases or disorders that may precipitate status epilepticus, including all conditions that might cause cortical structural damage (stroke, neoplasm, hypoxic injury, subarachnoid damage, trauma), intoxications, alcohol withdrawal, electrolyte abnormalities, infections of brain and/or meninges, and metabolic disorders such as hypoglycaemia, and hypothyroidism.

Myxoedema coma is a complication of long-standing untreated hypothyroidism. The term is largely a misnomer since most patients are not comatose. This condition is characterised by marked impairment of the central nervous system and of cardiovascular function.[2]

We report a patient with status epilepticus caused by severe hypothyroidism, who died despite treatment with thyroid hormone. To our knowledge there is only one other case report which describes a patient with myxoedema coma who also presented with status epilepticus, but that patient survived.[3]

CASE REPORT

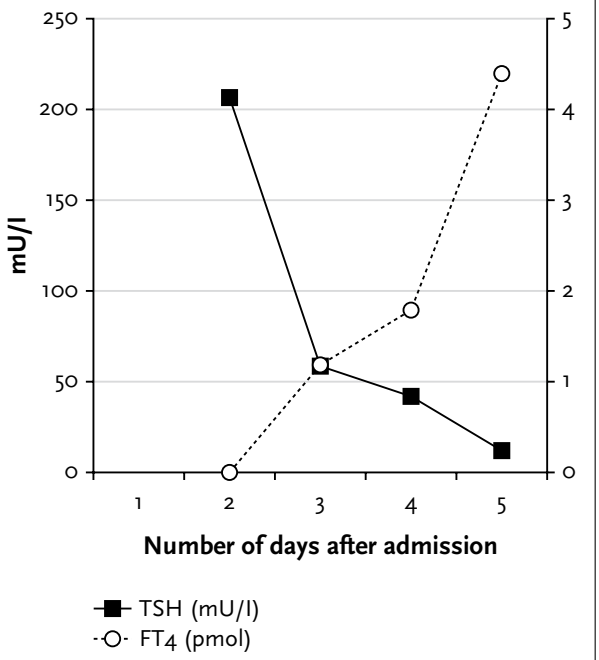
A 63-year-old female presented with convulsions and in coma. For six months she had been suffering from fatigue and lethargy. Five days before admission, she had developed problems with walking and muscle weakness. On the day of admission, she developed a seizure. Her medical history included hypertension and hypercholesterolaemia. On presentation, she had hypothermia of 34°C and a blood pressure of 160/110 mmHg. There were no signs of any infection at that time. She later developed hypotension (89/40 mmHg) with a heart rate of 100 beats/min. She had no peripheral oedema or oedema of her eyelids. Examination of the lungs, heart and abdomen revealed no abnormalities. Neurological examination showed a Glasgow Coma Scale score of $E_1M_1V_1$ and areflexia. Generalised tonic-clonic seizures were continuously observed.

Table 1 shows the most relevant laboratory investigations on presentation; no abnormalities were found despite a white cell count of 3.0 x 10^9/l, aspartate aminotransferase

Table 1. *Laboratory values on admission*

Variable	Value	Normal range
Haemoglobin (mmol/l)	8.5	7.5-10.0
Platelet count (x 10^9/l)	161	150-400
White-cell count (x 10^9/l)	3.0	4.0-10.0
Sodium (mmol/l)	140	135-145
Potassium (mmol/l)	4.0	3.5-5.0
Aspartate amino-transferase (U/l)	94	0-40
Alanine amino-transferase) (U/l)	98	0-45
Creatinine (umol/l)	96	50-100
Glucose (mmol/l)	7.9	4-7.7
Lactate dehydrogenase (U/l)	733	0-450
C-reactive protein (mg/l)	<1.0	0-6.0
Thyroid stimulating hormone (mE/l)	206	0.15-6.0
Free thyroxin (pmol/l)	<1.0	12.0-22.0
Arterial blood gas analysis		
Ph	7.14	7.36-7.44
pCO_2 (mmHg)	13.2	4.4-6
pO_2 (mmHg)	14.3	10.7-14.7
Bicarbonate (mmol/l)	33	22-29
Base excess (mmol/l)	0.6	-3.0-3.0

Figure 1. *TSH/FT4 curve (treatment was started two days after admission)*



94 U/l, and alanine aminotransferase 98 U/l. A thyroid-stimulating hormone (TSH) level of 206 mU/l and a free thyroxine (FT4) level of <1.0 pmol/l were determined two days after admission. An electrocardiogram (ECG) showed a sinus rhythm of 75 beats/min and some artefacts due to jerking of the extremities. There were no ECG signs of hypothermia such as an Osborn or J wave. Chest X-ray was normal. Brain CT scan and cerebral spinal fluid (CSF) examination revealed no abnormalities.

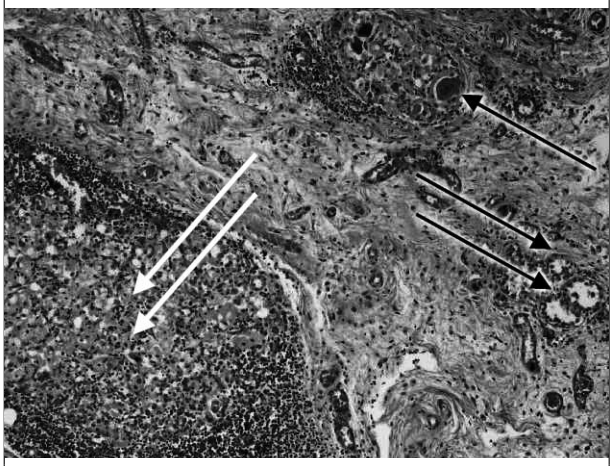
Because of hypoventilation, she was mechanically ventilated. She was treated with active re-warming using a hot air blanket and inotropic agents. Initially, convulsions were treated with diazepam 10 mg. Subsequently, intravenous phenytoin was started. Despite optimal antiepileptic treatment the seizures continued uninterruptedly and an EEG showed epileptic activity. Thiopental narcosis was induced for a period of three days.

Two days after admission, suppletion of thyroxine (T4) was started at a daily dosage of 100 µg and subsequently 150 µg daily, and triiodothyronine (T3) was given at 12.5 µg twice daily. *Figure 1* shows values of thyroid hormone after starting treatment. Because of the possibility of hypocortisolism, we administered hydrocortisone 100 mg intravenously every eight hours. After a few days, the patient developed a ventilator-associated pneumonia of her right lung. She was treated with cefuroxim 750 mg every eight hours intravenously.

Unfortunately, the patient showed no neurological improvement. She remained comatose with a Glasgow Coma Score of $E_1M_1V_{tube}$. After 14 days, we decided to stop the treatment because of a lack of improvement. Autopsy was performed. On histological examination the thyroid revealed complete atrophic follicles and an area of chronic inflammation with lymphocytes. The surrounding tissue showed fibrosis (*figure 2*).

Histological examination of the brain and the pituitary gland revealed no abnormalities.

Figure 2. *Thyroid tissue showing complete atrophic follicles (black arrow) and an area of chronic inflammation containing lymphocytes (white arrow)*



Between the area of inflammatory cells and atrophic follicles, fibrotic tissue is seen. (magnification 200 x)

DISCUSSION

Our patient suffered from severe primary hypothyroidism with status epilepticus, coma and hypoventilation as presenting symptoms. For several months she complained of fatigue and lethargy. On admission she had hypothermia, hypotension and was comatous with areflexia. Generalised tonic-clonic seizures with status epilepticus were observed.

Progression into myxoedema coma occurs when a hypothyroid patient's homeostatic mechanisms are disrupted (for example in the winter months). Multiple factors can precipitate myxoedema coma.[4,5] The more common precipitating factors include infection, particularly pneumonia, (uro)sepsis and cold exposure. In addition, several drugs may also precipitate myxoedema coma, including amiodarone, β-blockers, diuretics, narcotics (such as oxazepam), and lithium. In our patient, clear precipitating factors were not evident.

The neurological complications of myxoedema coma include alteration of mental status with slowness, decreased concentration and lethargy, headache, cranial nerve palsies, dysarthria, hoarseness, myopathy, neuropathy, reflex changes, ataxia and psychotic episodes.

Hypothyroidism and convulsions can occur in two different ways. First, late-onset epilepsy has been described in several patients who were later found to be hypothyroid and in whom convulsions stopped permanently when thyroid hormone was given.[6] In contrast, when convulsions accompany myxoedema coma they are usually preterminal. All nine patients reported in the literature with seizures who had myxoedema coma died,[7-9] except for one patient.[3]

The cause of epileptic seizure activity in hyperthyriodism is unknown. The electroencephalogram (EEG) in patients with hypothyroidism usually shows low-voltage alpha activity.[10] However, even pronounced hypothyroidism can exist with a normal EEG. It has been postulated that convulsions may be due to cerebral oedema secondary to expansion of the extracellular fluid volume. This may be related to inappropriate antidiuretic hormone (ADH) secretion and hyponatraemia, and hypoventilation with postanoxic encephalopathy. However, in our patient brain autopsy revealed no abnormalities.

The optimal mode of thyroid hormone therapy in patients with myxoedema coma is controversial, largely because the condition is so rare that there are no clinical trials comparing the efficacy of different treatment regimens. While fast increase of serum thyroid hormone concentrations carries some risk of precipitating myocardial infarction or atrial arrhythmias, this risk must be accepted because of the high mortality of untreated myxoedema coma. Some authors favour administration of T_3, because its biological activity is greater and its onset of action is more rapid than T_4. Others prefer T_4 because high serum T_3 concentrations during treatment have been correlated with mortality.[11]

It should be given intravenously because gastrointestinal absorption may be impaired.[12] The first dose of T_4 should be large – 200 to 400 µg – with the exact dose dependent on the patient's weight and age and the likelihood of complications such as myocardial infarction or arrhythmia. Thus, the dose should be reduced in lighter and older patients and those at risk of cardiac complications. For T_3 the same can be concluded. We decided to treat our patient with both T_3 and T_4. Because of the possible cardiac complications no loading dose of T_4/T_3 was given.

Hypothermia is a cardinal feature of myxoedema coma and is noted in approximately 80% of the patients. Correction of hypothermia requires external warming with blankets or a Bair hugger. However, one should be aware of hypotension because of the vasodilatory effect of rewarming. Sometimes inotropic support may be necessary. The susceptibility to vasodilatation is further aggravated by heart failure. Hypothyroidism may lead to decreased cardiac contractility, resulting in a reduction of stroke volume and cardiac output.

Electrolyte disturbances are common in myxoedema coma. The most common electrolyte abnormality is hyponatremia and it is usually due to impairment of free water excretion due to an inappropriate excess vasopressin secretion (SIADH) or impaired renal function.[13]

Hypoglycaemia may reflect underlying adrenal dysfunction. Patients with myxoedema coma are generally treated with stress dose corticosteroids. To rule out adrenal insufficiency, a random cortisol level can be obtained before initiation of therapy, or a rapid ACTH stimulation test can be performed.

Finally, supportive measures are extremely important in the treatment of myxoedema coma. These measures include treatment in an intensive care unit, mechanical ventilation if necessary, administration of intravenous fluids including electrolytes and glucose, correction of the hypothermia previously mentioned, and the treatment of any underlying infection.

The syndrome of myxoedema coma and convulsions represents the most extreme form of complicated hypothyroidism, and despite the best contemporary intensive medical care, is associated with substantial mortality ranging from 30 to 60%.[14] Factors associated with poor prognosis include advanced age, bradycardia, persistent hypothermia and the degree of consciousness (Glasgow Coma Scale).[15]

In our case there had been a delay of two days before starting thyroid suppletion. The most important elements in the treatment of myxoedema coma are early recognition, presumptive thyroid hormone replacement, corticosteroids and appropriate care.

This case showed us that if a patient suffers from status epilepticus associated with lethargy, fatigue and

hypothermia, myxoedema (coma) should be included in the differential diagnosis. Rapid determination of TSH, T4 and T3 must be performed and thereafter early institution of therapy.

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Netherlands
The Journal of Medicine

PHOTO QUIZ

A young man with nonhealing venous ulcers

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ABSTRACT

A 35-year-old man presented with nonhealing ulcers at an atypical location on his left foot, caused by a combination of venous insufficiency (after deep venous thrombosis) and arterial insufficiency. The underlying cause was Buerger's disease.

CASE REPORT

A 35-year-old man was admitted to our hospital because of nonhealing ulcers of his left foot. His medical history revealed deep venous thrombosis of his left leg, 14 years ago, and recurrent thrombophlebitis of this leg. The foot ulcers, which were painful, had been present for about one year without a provoking event. Apart from oedema of this leg since the thrombosis, he had no other symptoms. He had been smoking since puberty. No relevant other signs were present on physical examination. Venous insufficiency was suspected and confirmed by venous duplex ultrasonography. However, despite compression therapy and conventional wound care, the ulcers did not heal.

On admission, two ulcers were seen on his left foot (*figure 1*), with discrete oedema of this foot. Distal pulsations were present, except for the left dorsalis pedis artery, and no other abnormalities were found. Laboratory examination (including glucose, ANA, ENA, tests for antiphospholipid antibodies and homocysteine) was normal. A biopsy of the distal part of the left foot did not show any specific abnormalities. Since venous ulcers are not usually very painful, and mostly located on the medial aspect of the ankle, additional arterial tests were performed. Ankle-brachial pressure index was normal on both sides (left: 1.26, right: 1.23). Toe-brachial pressure index was normal on the right side (0.9), but too low on the left side (0.52).

Arteriography of the lower extremities showed segmental occlusions and many corkscrew collaterals, especially in the left leg (*figure 2*). A proximal source of emboli was excluded by echocardiography.

Figure 1. *Yellow discolouration on the left hand palm*

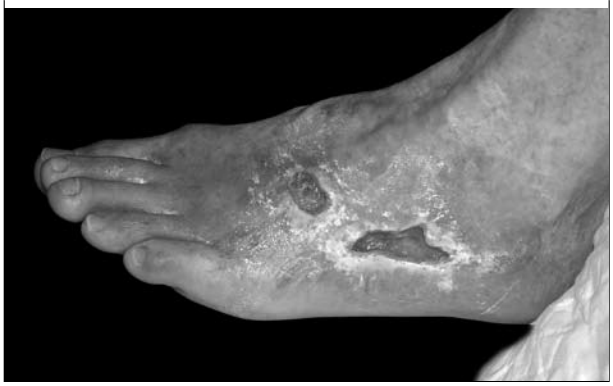
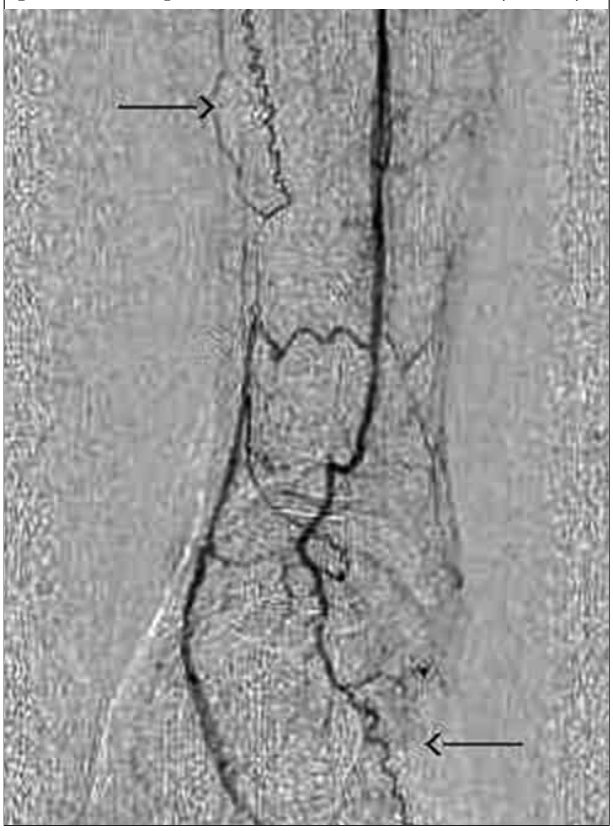


Figure 2. *Angiography of the left leg, showing occlusion of the tibial posterior artery, with distal supply from the peroneal artery and some corkscrew collaterals (arrows)*



WHAT IS YOUR DIAGNOSIS?

See page 209 for the answer to this photo quiz.

LETTER TO THE EDITOR

Yellow or orange hands as presenting signs of carotenaemia

Yellow discolouration was published recently in the photo quiz in the Netherlands Journal of Medicine.[1] Almost exactly the same clinical picture showing orange hands has been published previously.[2] In this previous study we reported carotenaemia presenting with orange hands due to excessive intake of β-carotene-containing vitamin drinks. The differential diagnosis of yellow or orange hands should include excessive dietary intake of vitamin drinks, lycopenaemia and riboflavinaemia. However, they were not excluded. Lycopenaemia is a probable diagnosis, because history mentioned high intake of processed tomato products, containing high amounts of lycopene. In addition, diagnosis was not confirmed by resolution of symptoms and normalisation of β-carotene levels following restriction of the culprit vitamin from the diet.

W. Miesen
Centre for Allergology, Twentegroep Hospital, Hengelo, the Netherlands

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Response from the authors

The most important observation in yellow-orange discolouration of the skin is the absence of scleral icterus. As Dr Miesen commented, the differential diagnosis is then limited to hypercarotenaemia, lycopenaemia, riboflavinaemia, and certain drugs, or vitamin drinks. A good review of carotenoderma has been written by Maharsak et al.[1] Carotenoderma may remain for weeks regardless of serum carotene levels, due to accumulation in the tissue. The importance of recognising this condition is mainly to explain to the patient what is happening and to avoid unnecessary examinations. Usually, hypercarotenaemia is caused by excessive dietary consumption of β-carotene. Some metabolic states may add to hypercarotenaemia due to impaired conversion of β-carotene into vitamin A or through hyperlipidaemia. Foods containing high carotene levels include carrots, spinach, peas, green beans, sweet potatoes, broccoli, mangoes, butter, eggs, milk and palm oil. Surprisingly, many green fruits and vegetables contain much more carotene than their yellow counterparts, with the yellow colour masked by the green chlorophyll. Processing of fruit and vegetables that results in breakdown of cell membranes significantly increases the bioavailability of the carotene. Our patient ate more than three big cans of processed vegetables daily (Hak, Zeist, the Netherlands: spinach, beans, peas) in addition to freshly cooked haricots verts, eggs, oranges, apples and also six tomatoes. He denied vitamin drinks. Lycopene, which is found in tomatoes, rosehips, pink guava, pink grapefruit and watermelon, may have added to the total clinical picture. However, we feel that the message of the photo quiz should be that a bizarre diet may surprise clinicians. Within eight days of his hospitalisation, β-carotene levels decreased to 0.95 μ/l. At follow-up, the patient was eating a normal diet and showed no yellow discolouration.

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Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands, *corresponding author

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SPECIAL REPORT

Awards for the best articles published in 2005

The Editorial Board

Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

In 2004, the Netherlands Journal of Medicine started to award prizes for the best articles in the Journal.[1,2] The main goal of awarding these prizes is to foster a bond between the readers, authors and editors of the Journal. Moreover, it also aims to enhance the quality of the submitted articles, which serves us all. This year, the jury consisted of P.W de Leeuw, A.E. Meinders, and B. Hylkema and they had the difficult task of selecting the best paper from the following categories: case report, review article, and original article. The jury cuttingly remarked that the quality of articles published in the Journal showed a solid upward trend, which made the selection process difficult.

REVIEW ARTICLE

Review articles are highly appreciated by our readers and are central to the mission statement of the Journal.[3] A well-written review provides the readers of the Journal with a comprehensive overview on topical issues of immediate clinical relevance. The jury selected articles that scored best on items such as clarity, educational value, quality of the illustrations, and relevance for the clinical practitioner. The review article of Dr S. Bovenberg *et al*. summarises the clinical pharmacological aspects of dehydroepiandrosterone (DHEA).[4] DHEA treatment is thought to improve mood and quality of life, and Dr Bovenberg's balanced review focuses on the indications and possible use of DHEA in clinical practice.

CASE REPORT

Articles from this category were judged on items such as the description of the case, novel pathophysiological aspects, and clinical impact. The case report by Dr T. Jansen on a patient with pulmonary symptoms and cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA) seropositivity describes a 40-year-old man who was suspected of having Wegener's disease because of upper airway symptoms and presence of c-ANCA.[5] The author rejected the diagnosis of Wegener's disease despite these findings and went on to search further. Specificity analysis revealed that he was negative to antibodies for proteinase-3, but positive to myeloperoxidase and concluded that the c-ANCA was falsely positive. This article is a prime example of cunning clinical reasoning and was commended for this aspect by the Jury members.

ORIGINAL ARTICLE

Articles from this category were judged for their originality, scientific and clinical relevance, and whether a lucid hypothesis was present. The original article by Dr E. Bierdrager *et al*. focuses on the palliative treatment of patients with neoplastic superior vena cava syndrome.[6] They chose to treat these patients by inserting a self-expanding stent in the superior caval vein and describe their experience in 15 patients. The authors conclude that stenting of the superior caval vein prior to antitumour therapy is feasible, can be performed without major complications and probably provides a faster symptom response than conventional treatment with radiation therapy or chemotherapy.

The editor-in-chief Professor Anton Stalenhoef awarded the prizes at the 2006 Convention for Internal Medicine (Internistendagen) on 28 April 2006 in Maastricht, the Netherlands. Ultimately we hope that these high-quality papers will make it to the Journal's best cited 'hit list'.[7]

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ANSWER TO PHOTO QUIZ (ON PAGE 206)

A YOUNG MAN WITH NONHEALING VENOUS ULCERS

Findings were suggestive of Buerger's disease (thromboangiitis obliterans). This disease is characterised by the occurrence of segmental thrombotic occlusions of the small and medium-sized arteries in both upper and lower extremities and classically occurs in young male smokers. Not only arteries are affected, but many patients (approximately 40%) also suffer from or have a history of superficial thrombophlebitis. This thrombophlebitis can extend into the deep venous system, as is illustrated by the presented case.[1]

Other diseases must be excluded, especially vasculitis and atherosclerosis. Noninvasive vascular testing may suggest arterial occlusive disease. However, since the disease is usually confined to the distal part of extremities, sometimes only toe pressures may be abnormal, as in the presented case. Arteriographic findings may be suggestive. Histopathological examination can provide definitive proof, but is often inconclusive, especially when lesions have been present for longer periods. Thus, the diagnosis is usually made using a combination of the clinical and arteriographic signs described above, in the absence of other possible causes.[2] Treatment consists of discontinuation of smoking and low-dose acetylsalicylic acid. In case of critical limb ischaemia intravenous iloprost (a prostaglandin analogue) may be used.[3]

In our patient, this regimen, in combination with compression therapy (avoiding too high compression pressures), resulted in healing of the ulcers.

DIAGNOSIS

Combination of venous and arterial insufficiency, probably both caused by Buerger's disease.

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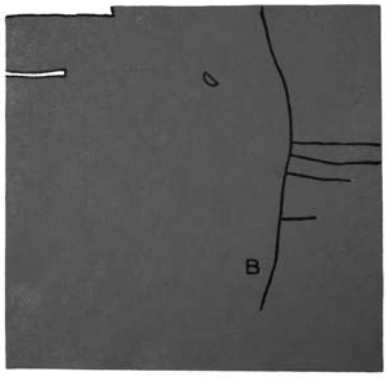
ABOUT THE COVER



Cees Andriessen makes a direct connection between writing and graphics. His communicative stance is visible in the symbiosis of the language of picture, shape and symbol which not only wants to be looked at but, above all, read.

Andriessen emphasises the similarities between the literary process of writing and the conversion of forms of language into a language of forms and shapes. The exceptional level of abstraction is juxtaposed in a special way to the readability of his work. Similarly, the sublimated simplicity of the visual language is balanced by the underlying philosophical depth.

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

Manuscripts
Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

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

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

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

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

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

Keywords: Include three to five keywords.

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

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

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

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

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

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

Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al. Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against the reference list after your manuscript has been revised.

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