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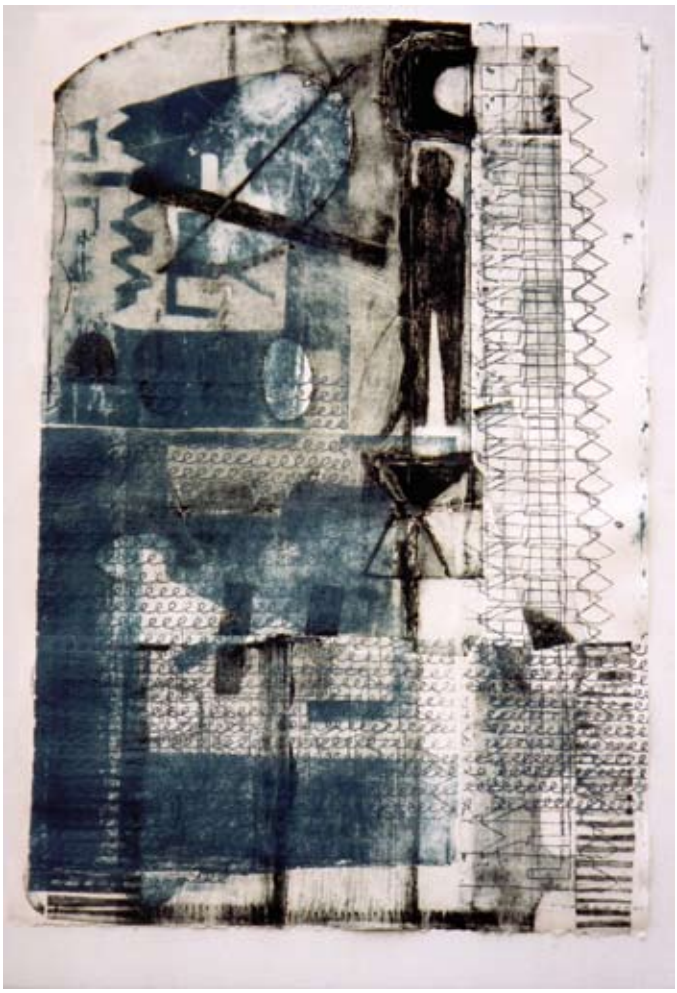

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EDITORIAL

Osteoporosis

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In recent years several guidelines on the prevention and treatment of osteoporosis have been published. In the Netherlands two professional organisations have updated their earlier documents. The Dutch Institute for Healthcare Improvement, CBO, published its Second Revised Guideline on Osteoporosis in 2002.[1] The Dutch College of General Practitioners (NHG) followed in 2005 with a revised osteoporosis guideline.[2] Both documents reflect the vast increase in knowledge on the diagnosis, epidemiology, prevention and treatment of osteoporosis in the past decades.

Bone densitometry, mostly by dual energy X-ray absorptiometry (DEXA), remains a cornerstone in the assessment of fracture risk and in the selection of patients for treatment with bone-active protective agents such as bisphosphonates. The two Dutch guidelines mentioned above are in accordance on the indication for bone densitometry. They recommend a DEXA is performed in selected individuals with increased fracture risk based on other risk factors. The risk score included in the NHG guideline is summarised in *table 1*. Bone densitometry is recommended for patients with a risk score ≥4.

Table 1. *Indications for bone densitometry (DEXA is recommended for patients with total score ≥4)*[2]

Risk factor	Score	Sex
Existing vertebral fracture [a]	4	Male and female
Use of oral glucocorticoids [b] (for ≥3 months at a dose (prednisolone) ≥7.5 mg/day)	4	Male and female
Fracture after age 50	4	Female
Age >70 years	2	Female
Age >60 years	1	Female
Hip fracture in first-degree relative	1	Female
Body weight <60 kg	1	Female
Serious immobility	1	Female

[a] **Preventive treatment indicated for patients with more than one vertebral fracture without bone densitometry;** [b] **preventive treatment indicated for patients with a dose (prednisolone) ≤15 mg/day.**

In this issue of the Journal, Schurink *et al.* report on a study of osteoporosis case-finding that was performed between October 2003 and June 2004.[3] They studied patients aged ≥50 years, who had sustained a non-vertebral fracture in 2001, three years before the study.[3] Eventually 88 out of 273 patients were included in the study. About half of these patients also had at least one other risk factor. Bone densitometry had already been performed prior to the study in only 12 patients. DEXA scans were carried out as part of the study in all 88 patients. Low T-scores below -2.5 were found in 45 patients. These results confirm the high prevalence of osteoporosis in patients above the age of 50 with a fracture.

The results also suggest that the doctors caring for these patients did not employ an active strategy to detect patients at risk for osteoporosis, as recommended by the 2002 revised CBO guideline. This is in accordance with the low frequency of osteoporosis treatment after fractures reported in the literature.[4-8]

The revised NHG guidelines were published after the present study was carried out. *Table 1* shows that bone densitometry should have been considered for the female patients (69 out of 88) in the study by Schurink *et al.*[3] according to the NHG guideline. The present study does not allow any conclusions on adherence to the NHG guideline. The reported low adherence to other osteoporosis guidelines does not allow for optimism.[4-8]

The authors compare their results with their experience in a Fracture and Osteoporosis outpatient clinic. They have previously reported a much higher guideline adherence in this setting, 75% of the patients at risk being examined for osteoporosis.[9] They strongly advocate the idea that the physician who treats the fracture should be responsible for initiating osteoporosis screening and subsequent treatment if necessary. The NHG guideline (note 1) also states that the physician who detects and treats the fracture should ideally also be responsible for osteoporosis screening and initiating treatment.[2] However, other roles with a more active part to be played by the general practitioner (GP) can be agreed upon depending on

regional preferences.[2] One of the reasons to consider such a role for the GP would be that the GP remains responsible for the continuation of preventive treatment and that compliance to osteoporosis treatment regimens started outside family practice can be quite low.[10] An active part in initiating treatment could perhaps contribute to achieving higher levels of compliance of preventive treatment.

The reasons for low osteoporosis guideline adherence have not been studied extensively. Solomon *et al.* found that patient age ≥75 or <55 years, male sex and the presence of more than one comorbid condition adversely affected guideline adherence. Female doctors followed osteoporosis guidelines more often than male doctors.[11] More studies are needed to more fully comprehend the factors that influence guideline adherence in order to design appropriate implementation strategies. In the meantime, regional agreements should be reached between GPs, surgeons and other involved medical specialists on how to diagnose and treat osteoporosis in patients with a low-energy fracture after the age of 50. These agreements should be based on the current guidelines and include statements on the specific roles of all parties in the evaluation of patients, the initiation and continuation of therapy and on the communication between GPs and medical specialists. The agreements should also provide a means of evaluating practice and quality of care.

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EDITORIAL

Clinical incidents and risk prevention

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INTRODUCTION

Over the past two decades a series of medical disasters have created public concern. One of the most widely disputed and analysed scandals was the one that took place at the Bristol Royal Infirmary, usually referred to as 'the Bristol case'. This tragedy is thought to have at least doubled the mortality rate in young children after paediatric cardiac surgery for over more than a decade.[1]

Much has been made of the way in which the principal actors (two paediatric cardiac surgeons) and their medical and managerial colleagues initially denied the situation and failed to recognise that their clinical activities had and were placing lives at risk.[2]

Unfortunately the Bristol case was not just an isolated incident. Since the inception of the National Health Service (NHS) in the UK in the 1970s, more than 30 NHS public inquiries had been conducted up to 2001 to address catastrophic failures in patient care and this number is rapidly increasing.[3]

And things do not only go wrong in the UK. Most countries in Europe and important regulatory bodies in the US and Australia report on problems in the field of patient safety.[4-6]

Also the Netherlands has its share of failures. Recent interventions and analyses of hospital misconduct undertaken by the Inspectorate in the Netherlands (the cardiothoracic surgeons at the Radboud University Medical Centre in Nijmegen, the surgeons at the Maas Hospital in Boxmeer and the Intensive Care doctors at the St Jans Hospital in Weert) show communication failure and deficits in teamwork were important determinants of harm,[7] a finding that is affirmed by investigations elsewhere.[8] For example, a survey in the Netherlands showed that overt conflicts between medical specialists threaten the quality of patient care in at least one third of the hospital departments.[9]

What can medical specialists learn from these cases? First, take a close look at your practice, your department and your own hospital. Are you sure this could not happen to you? Second, if you feel or think that everything is safe, do you have the numbers available to confirm that you are indeed safe?

In this editorial, I will address the subject of patient safety, with a focus towards the hospital setting. What are the most important types of medically unsafe practices that may confront us? Do we know how often they occur and the consequences? Do we know how to prevent them? What is the evidence to support these preventive activities? How can we measure and monitor progress?

PATIENT SAFETY ON THE AGENDA

Eight years ago, the Institute of Medicine (IOM) called for a national US effort to make American health care safer.[10] They reported that as many as 98,000 patients die annually due to medical errors. Ever since, patient safety has become a hot topic for journalists, health care managers and concerned citizens, but much less so for health care professionals. They are primarily concerned about being blamed, punished and suspended.[11]

Instead they should take the lead in medical error prevention and promote a culture of safety. So let us see what is known about error and preventive actions.

THE FIGURES

The epidemiology of accidents in health care is well known. The prevalence of iatrogenic harm in hospitalised patients ranges between 3.7 to almost 16%.[12,13] Besides the burden placed on patients and their relatives, the knowledge that half of these events are preventable and the enormous costs of dealing with the resulting injury seriously challenges the health care system. The IOM report estimated that 17 billion US dollars of direct health care costs annually are related to medical injuries. In patients involved in medical complications the mean hospital stay has more than doubled (up to a mean of 14 days) while the costs have tripled.[14]

DYSFUNCTIONING

Apart from the rather constant numbers of complications that seem to be related to Western health care delivery, disaster medicine resulting from serious misconduct may occur. Disasters may become visible by, for example, a high incidence of complaints from patients, high reporting of incidents by health care providers or high complication or death rates from registrations. These reporting systems are not very sensitive, as history shows. Usually it takes a long time before the disaster is recognised, and even longer before the problems are taken seriously and tackled. The Bristol Royal Infirmary tragedy already mentioned is exemplar.[15] Recently, systems to detect and 'treat' dysfunctioning doctors have been developed,[16] and are gradually being introduced in the US and UK. It is probably even more difficult to detect group dysfunctioning or conflicts among medical specialists, as doctors usually have a group code to try to keep the problems among themselves.

IT MAY HAPPEN TO ANY OF US

In the past ten years, medical errors are repeatedly occurring in hospitals all over the world. These can no longer be considered incidents, but seem part of common practice. Numerous studies increasingly show that between 30 and 50% of patients do not receive the optimal care they deserve.[17] It is only a matter of time before over-, under- or misuse leads to error that is reported or detected.

THE RESPONSE

What must be done within the health care system, by the health care professionals and by management? What actions can make your health care safe?

SAFETY PLANS AND SYSTEMS

As a result of the IOM report, only a few US hospitals did not take any action.[18] A survey in 2004 showed that while 74% of American hospitals reported full implementation of a patient safety plan, just under 9% reported no plan at all. The area of surgery showed the greatest level of patient safety systems. What was surprising was the low level (34%) of fully implemented computerised physician order entry systems for medication. *Table 1* shows an overview of systems developed and used in US hospitals.

Most hospitals in Western Europe are currently introducing all manner of risk management activities and systems. An example is the critical incident reporting about (near) misses that has been introduced in almost all the hospitals in the US and UK.

Table 1. *Patient safety systems*

Variables
Plans, policies and programmes
• Patient safety committee
• Patient safety officer
• Patient safety programme budget
• Significant adverse events reported to patients/families
• Trend analyses conducted on incidents
• Process redesigns monitored for effectiveness
• Written patient safety plan as part of quality improvement plan and developed on safety assessment results
• Root cause analysis after (near) miss, with actions taken based on the analysis and findings
• American Hospital Association self-assessment documents used
Leadership and environment
• Adverse event actual/potential assessed
Data and computerisation
• Clinical codes from medical records used to monitor patient safety
• Quality improvement programme that monitors injuries and adverse events using discharge data
Surgery
• Preanaesthesia patient assessment and anaesthesia plan
• All preprocedure diagnostic studies included in chart prior to surgery
• Primary surgeon verbally confirms side for operation, limb and/or site marked with witness
• Identification of equipment malfunction
• Surgery technical performance errors
Medications
• Full-time pharmacist on staff
• Nonpharmacists have access to medication after hours when no pharmacist is available
• Safety measures for look-alike drugs
• Safety measures for sound-alike drugs
• Safety measures for spelled-alike drugs

A critical look at these systems shows great variations in what is reported and how the data are being used.[19] No research has proven its effectiveness in health care[20] although the reporting and the actions based on it have successfully reduced the number of aviation incidents[21] and accidents in other types of industries.

One of the problems is the poor level of reporting.[22] The blame and shame culture and the fear for litigation, dismissal and suspension that pervades our medical system frustrates the implementation of such a critical incident reporting.[23-25] Anonymous reporting to an independent body at a regional (or national) level may encourage reporting;[26] however, on the one hand it may lead to irresponsible accusations and on the other may overlook local problems. Safe reporting, which means that the reporter cannot be legally accused on the basis of his own report, seems the solution but reporting incidents is not enough. Only proper investigation leading to appropriate preventive action seems worthwhile. Unfortunately the evidence on the best and most cost-effective methods stops here and intuition takes over.

SAFETY MANAGEMENT SYSTEMS

Managers and commercial firms have taken the lead and try to persuade hospitals to take over their (often time-

consuming or costly) system or method. No results are available yet from properly designed studies of all these systems. So all actions may be classified as premature, although a sense of urgency forces hospital management to take some kind of action, even if no evidence is available. Systems used include the widely introduced systematic analysis of severe reported events by root cause analysis.[27] Root cause analysis follows a highly structured process of triage questions throughout the health care system, tracing some fundamental problems over a series of events. It is time consuming, retrospective in nature and simplifies events. Therefore, the American National Centre for Patient Safety developed a more proactive method (HFMEA; Healthcare Failure Method and Effect Analysis) for the functioning of a process delivered by a multidisciplinary team. Nonetheless, HFMEA is also time consuming while it is not known whether its deployment really prevents unsafe care.

A SAFETY CULTURE

In accordance with high-risk industries it is recommended that health care organisations should regularly assess their 'safety culture'. Safety culture is considered the product of individual and group values, attitudes, perceptions, competencies and patterns of behaviour that determine the commitment to, and the style and proficiency of, an organisation's safety management. From this definition it is already clear that a safety climate will be difficult to measure, an opinion secured by a systematic review that showed the weaknesses of measurement instruments.[28] And if a valid and reliable instrument can be designed in the future, the next problem will be which strategy should be used for improvement.

PRACTICE VERSUS SYSTEMS

So let us get out of management language and systems and return to the quality of patient care itself. What practices will most endanger patients and what practices will most improve safety?

After the IOM report the US president ordered a government-led wide feasibility study, which directed governmental agencies to implement the recommendations. As a consequence the Agency for Health Care Research (AHRQ) determined a list of 'best practices' for all clinicians, with the evidence level included.[29]

Three problem areas emerged as the most important health care issues occurring most frequently with a high strength of evidence to support them:

1. Anticoagulation therapy to prevent deep venous thrombosis (the number one rating).
2. Antibiotic prophylaxis to prevent surgical infections.
3. Use of pressure-relieving materials to prevent pressure ulcers.

The use of perioperative β-adrenoceptor blockers in cardiac patients, maximum sterile barriers (with antibiotic or impregnated or sterile silver alloy-coated catheters and if indicated ultrasound guidance) during catheter insertion, informed consent procedures from patients, the prevention of ventilator-associated pneumonia by continuous aspiration of subglottic aspirations (CASS) with semi-recumbent positioning all have a high level of evidence. Patient self-management using home monitoring devices during chronic long-term anticoagulant therapy and various nutritional strategies in (abdominal) surgery patients (with selective decontamination of the digestive tract), computer monitoring of adverse drug events (due to analgesics, potassium, antibiotics, heparin), information delivery if transfer of the patient is indicated and adequate pain management also showed a high strength of evidence.

Management of falls, postoperative pain, delirium and contrast-related renal failure are recommended with a medium strength of evidence.

Although they lacked sufficient rigorous evidence of efficacy unit dosing, the introduction of a computerised physician order entry (CPOE) and bar coding were placed in the top category for improvement. This was followed by localising specific surgical and other procedures to high-volume centres, improved hand washing compliance and clinical pharmacist consultation services, all with a medium strength of evidence.

The recommendation to introduce CPOE, bar coding and pharmacist consultation is probably due to the high frequency of medication error in the Boston Medical Practice Study.[30]

Overlooking the recommendations, technical approaches prevail. These technical advances are probably easy to study, while system errors or easy practical solutions have received little research funding. Simple practical 'common sense' solutions are not mentioned because they have not been studied in randomised controlled trials.[31]

Examples of these common sense solutions are the removal of concentrated potassium chloride from nursing units, unit dosing instead of bulk dosing, the requirement of duplicate independent calculating and reading when intravenous drugs are prepared and administered, and educating patients about accurate use of their medications. Leape *et al.*[31] plead for a combination of evidence-based solutions with a common sense approach, to be tested later on, and accepted practices from other industries.

KNOWLEDGE FOUNDED ON MEASUREMENT

One key barrier for progress is the paucity of proven safety measures in the literature. To identify problems and to demonstrate improvement over time robust measures

should be available. In the early 1990s, Iezzoni *et al.*[32] developed a Complication Screening Programme to screen systematically for quality gaps, using administrative data. Soon after, the Agency for Healthcare Research and Quality (AHRQ) developed a similar set.[33]
In the lately 1990s, hospitals in the State of New York started using measurements extracted from discharge records.[34]

AUTOPSY

Discussion on the results of autopsy is the oldest tool and still the gold standard to evaluate medical accuracy in diagnostics and therapeutics. After the ancient Greeks, who used it to study human anatomy, autopsy became common practice in Europe during the Renaissance and was gradually linked to diseases and an evaluation of clinical handling. Unfortunately autopsy rates are steadily falling as most clinicians are convinced that the new imaging techniques such as computerised tomography, magnetic resonance imaging and positron emission tomography scanning, which can also be combined with functional studies, offer clinicians all the critical information needed and seem to have made pathological examinations after death unnecessary.[35]
Over and over it has been shown that this impression is wrong. For example Aalten *et al.* recently showed that in nearly 40% of autopsies in geriatric patients, major discrepancies were seen between clinical diagnosis and autopsy findings. These findings stress the important role of autopsy as a quality instrument to detect diagnostic errors.[36]

SCREENING OF MEDICAL RECORDS

Record review is one of the primary methods to assess the incidence of adverse events. This method is time consuming, its reliability depends on the training and experience of the (independent) assessors and the accuracy and completeness of the patient records. Yet it has provided a more complete indication of the incidence of adverse events than other reporting systems.[37] A new modular review form is suggested, which makes it possible to benchmark the results.[38]

COMPLICATION REGISTRATION

Having information regarding unwarranted results of diagnosis or treatment provides the information to develop interventions to prevent them. Such a complication registration should be supplemented by a statistical analysis to identify preventable high frequency complications and contributing factors. During the structured discussion meeting that follows, a redesign of the process that influenced the event and a literature search regarding the evidence of improvement measures are important.[39]

SAFETY INDICATORS

Recently the AHRQ promulgated a set of patient safety indicators (available at: http://www.qualityindicators.ahrq.gov). The Institute for Health Care Improvement developed trigger tools for measurement of harm.[40] A similar indicator tool has been developed for preventable drug-related morbidity in general practice.[41] To design reliable indicators for unsafety these indicators should fulfil the criteria of a solid diagnostic instrument. Safety indicators should be valid, reliable and feasible.[42] Future research will show whether the proposed safety indicators comply with these requirements.[43]
Table 2 gives an overview of the safety indicators as measured in 430,552 US patients, registered in the Veterans Administration. The precise definitions of the numerator and the denominator can be found in the report by McDonnald *et al.*[44]

BEST PRACTICES

Yet, why all these time-consuming registrations? The epidemiology of incidents is well known and the success of the method depends on the conclusions and the subsequent measures taken.
Some warn that too much effort is being devoted to measures of injury rather than implementing known methods that reduce injury, because it is argued that the amount of knowledge about how medical care can be made safer is already so comprehensive that these strategies should be implemented now.[45] For example standardised, electronic guideline-driven dosage protocols in high-risk medication areas have already been proven effective in diabetes,[46] and in anticoagulant care.[47]
The Joint Commission on Accreditation of Health Care Organisations has a very informative and practical website (http://www.jointcommission.org) with a site dedicated to patient safety. It contains the 14 US 2006 national patient safety goals. These are related to patient identification, medication and surgery safety, prevention of infections, falls and pressure ulcers, communication and patient involvement. Their website presents facts, questions asked, practical and simple advice, implementation strategies and background and teaching information. So it is possible to start now, without a great burden on personnel or resources.

A PRACTICAL APPROACH

If you feel you should start now, a practical approach is advisable. Let each medical speciality in a hospital select its five topics regarding medical error from literature by using three criteria (prevalence, resulting damage and preventability). Next construct or take over two process

Table 2. *Rates of patient safety indicator (PSI) events in VA* data#*

		Numerator	Denominator	PSI
1	Complications of anaesthesia	55	97,482	0.56
2	Death in low mortality DRGs	178	55,079	3.23
3	Decubitus ulcer	3207	208,097	15.41
4	Failure to rescue	3316	21,318	155.55
5	Foreign body left in during procedure	73	430,536	0.17
6	Iatrogenic pneumothorax	469	402,185	1.17
7	Infection due to medical care	817	345,442	2.37
8	Postoperative hip fracture	81	71,053	1.14
9	Postoperative haemorrhage or haematoma	315	97,479	3.23
10	Postoperative physiological and metabolic derangements	77	40,788	1.89
11	Postoperative respiratory failure	107	31,207	3.43
12	Postoperative pulmonary embolism or deep vein thrombosis	1262	97,231	13.00
13	Postoperative sepsis	106	17,283	6.13
14	Postoperative wound dehiscence	129	20,115	6.41
15	Technical difficulty with procedure	1216	430,524	2.82
16	Transfusion reaction	3	430,536	0.007

***VA = Veterans Administration. DRG = diagnosis-related groups. #Data extracted from Jonantgen, et al.[33]**

indicators and one outcome indicator connected with the topic. Measure the results and give feedback in a comparative way[48] after case-mix correction. Let the responsible person or group comment on the results if these deviate more than two standard deviations (SDs) below average. Subsequently, let the group be peer-reviewed by the best national, regional or local performers regarding this issue. With their advice an improvement plan is formulated and feedback is given on the formulated targets within an agreed time frame.
This looks simple, cheap and attractive for care providers. Is it better or more cost-effective than the managerial plans? Let's find out.

CONCLUSION

In conclusion the research agenda in this area is clear. There is a need for much more quantitative research comparing the several approaches that are now being introduced because of the sense of urgency. Comparative studies in high incident areas such as in surgery, obstetrics or the medication process are warranted. The prevention of iatrogenic harm is a research priority, not only for doctors, allied health professions or nurses, but also to their patients and society. The failure to carry out such research is a disgrace to all of us.

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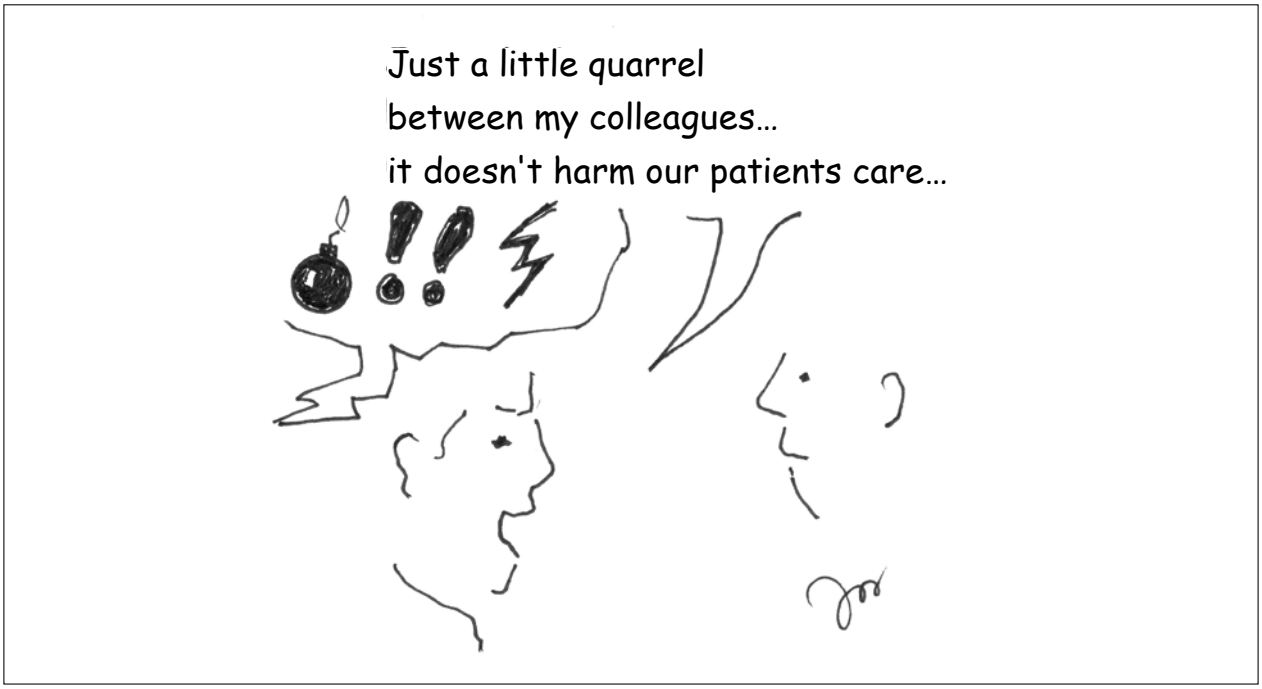

Wollersheim. Clinical incidents and risk prevention.

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REVIEW

Adrenocortical carcinoma

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ABSTRACT

Adrenocortical carcinoma is a rare disease with a poor prognosis. Patients can present with a hormonal syndrome or with general symptoms from an abdominal mass. The pathogenesis is unknown. Sometimes the adrenocortical carcinoma is associated with tumour syndromes such as the Beckwith-Wiedemann and Li-Fraumeni syndrome; however, most tumours are sporadic. Using one of the international classification methods, histopathological research can in almost all cases distinguish between adrenocortical adenoma and carcinoma. Complete surgical resection is the treatment of choice for adrenocortical carcinoma. Mitotane is given when surgery is not possible, after incomplete resection or for metastatic disease. Frequently used chemotherapeutic combinations are etoposide, doxorubicin, cisplatin and mitotane (EDP/M) and streptozotocin and mitotane (Sz/M). International and national cooperation has resulted in a randomised trial aimed at determining a standard therapy in advanced adrenocortical carcinoma. The Dutch Adrenal Network is a national cooperation of endocrinologists, pathologists and oncologists from all eight academic centres and Máxima Medical Centre. The network combines knowledge and expertise and gives patients the opportunity to receive optimal treatment in their own district.

KEYWORDS

Adrenocortical carcinoma, therapy, treatment

INTRODUCTION

Adrenocortical carcinoma is a rarely occurring disease. The annual incidence is approximately 1-2 individuals per million.[1] The poor prognosis and the scant knowledge and experience of physicians pose a major problem for both physicians and patients. Therefore, it is important to centralise knowledge of and experience with adrenocortical carcinoma, so that patients get the best possible treatment and care.

This article reviews new developments in both treatment options and national/international cooperation for patients with adrenocortical carcinoma. First the clinical features, diagnostics, pathology and pathogenesis of adrenocortical carcinoma will be discussed, followed by treatment options and a description of national and international cooperation and the related trials.

Finally the Dutch Adrenal Network will be discussed, which aims at optimalisation of treatment and care of patients with adrenocortical carcinoma in the Netherlands.

CLINICAL PRESENTATION

Approximately 60% of adrenocortical tumours are hormonally active. Cushing's syndrome alone or a mixed Cushing's syndrome with virilisation is the most frequent presentation.[1-3] This can be a rapidly developing disease with skin atrophy, hyperglycaemia, muscle weakness, hypertension and psychiatric disorders. Androgen-secreting adrenocortical carcinoma presents with male pattern baldness, low voice, hirsutism and oligoamenorrhoea in women. Oestrogen-secreting tumours present with gynaecomastia and testicular atrophy in males.[4]

Hyperaldosteronism, characterised by hypokalaemia and hypertension, may also be present.[5] However, severe hypokalaemia can also be caused by elevated cortisol secretion.

Patients with a hormonally inactive adrenocortical carcinoma often present with local symptoms of the tumour itself, including abdominal fullness, pain and gastrointestinal complaints such as nausea and vomiting.[5]

Adrenocortical carcinomas are increasingly detected as an incidentaloma during abdominal imaging. A minority present with fever and weight loss and in a few cases a palpable mass can be felt on physical examination.

Adrenocortical carcinoma tends to spread by both the haematogenous (most frequently the lungs, followed by the liver and sometimes the bones), and the lymphogenous route (to regional and paraaortic lymph nodes).[6] Metastases to the other adrenal, or bilateral adrenocortical carcinoma, may be found in 4% of the cases.[7]

PROGNOSIS AND STAGING

Stage 1 and 2 describe tumours of less or more than 5 cm, respectively. Stage 3 describes locally invasive tumours or tumours with regional lymph node involvement. Tumours invading adjacent organs or tumours with distant metastasis are categorised as stage 4.[7]
The average survival time of untreated patients is 2.9 months and largely depends upon the tumour size.[8] With treatment the five-year survival rates are 60% for stage 1, 58% for stage 2, 24% for stage 3, and 0% for stage 4.[9]

DIAGNOSTIC EVALUATION

The diagnostic evaluation of adrenocortical carcinoma depends upon the clinical presentation. Cushing's syndrome at time of presentation requires measurement of the urinary cortisol excretion for 24 hours, early morning cortisol after 1 mg dexamethasone at 23.00 hours the night before (known as the 1 mg overnight suppression test), or the late night (salivary) cortisol level. A positive (elevated) result of one of these tests confirms Cushing's syndrome. Low levels of plasma ACTH are seen with the ACTH-independent, adrenal variant of Cushing's syndrome.[10]
Gas chromatographic separation of 17-ketosteroids reflects an abnormal steroidogenesis which is characterised by increased levels of cortisol precursors such as 17-OH-progesterone and 17-OH-pregnenolone. An abnormal gas chromatography with excess excretion of the cortisol precursors establishes the clinical diagnosis of adrenocortical carcinoma.
Elevated plasma levels of dehydroepiandrosterone sulphate (DHEAS) and testosterone in women and 17-β-oestradiol in men are markers for adrenocortical carcinoma, although their specificity is unknown.[11]
CT scan or MRI is the best diagnostic procedure for patients presenting with pain or a palpable tumour at physical examination.[5] On CT scan or MRI benign and malignant disease can be distinguished based upon the size, irregularity and inhomogenicity. However, in the end, adrenocortical carcinoma is a histological diagnosis.
In 30% of adrenocortical carcinomas calcifications are visible. Adrenocortical lesions with a density of more than 10 Hounsfield units on a non-contrast CT scan, or less than 50% washout of contrast after 15 minutes together with a density of more than 35 Hounsfield units, are suspect for malignant tumour.[7] FDG-PET scan can detect locoregional tumours and metastatic disease.

PATHOLOGY

At the time of clinical presentation it is difficult to differentiate between benign and malignant disease unless evidence of metastatic disease is present. Several histopathological characteristics are useful for differentiating benign from malignant disease. There are two important classification systems by von Weiss and van Slooten, respectively. In the Netherlands the classification by van Slooten is usually used. Internationally the Weiss score is the most widely used tool.[12-14] The classification by van Slooten is based upon the following parameters: regressive nature, conservation of normal histology, nuclear atypia, nuclear hyperchromasia, structure of nucleoli, mitotic activity and capsular invasion.[12] The mitotic activity is the most important parameter.
Tumour markers such as Ki-67, inhibin, melan-A and calretinin are detected with immunohistochemical examination; however, they have a low specificity for adrenocortical tumours.

PATHOGENESIS

The aetiology of adrenocortical carcinoma is mostly unknown, as are the risk factors. Sporadic adrenocortical carcinoma is most common; however, hereditary syndromes do occur as in the Beckwith-Wiedemann syndrome, Li-Fraumeni syndrome, Carney complex, MEN-1 syndrome and McCune-Albright syndrome.[15,16] The Li-Fraumeni syndrome is caused by inactivating mutations of the p53 tumour suppressor gene.
The gene defect responsible for the Beckwith-Wiedemann syndrome is localised on the 11p5.5 locus and leads to tumours such as Wilms tumours, neuroblastoma, hepatoblastoma and adrenocortical carcinoma. The 11p5.5 locus contains the IGF-II, H19 and the p57/Kip2 genes, the last one coding for the p57 tumour suppressor protein.[17] ACTH receptor mutations are not important in the pathogenesis of adrenocortical carcinoma. The role in the carcinogenesis of decreased ACTH response is unclear.

THERAPY

Surgery

The best treatment for adrenocortical carcinoma is complete resection of the tumour. The overall five-year survival rate after total resection is 49%, in contrast to

9% after incomplete resection.[18] When total resection is not possible, debulking is a therapeutic option to decrease excess hormone production, and is possibly associated with a better overall survival compared with nonsurgical treatment. Resection of recurrent disease is advised because of the increased overall survival.[5]
The risk of capsular damage is the same for malignant and benign tumours; however, it increases with laparoscopy. This is more of a problem for malignant tumours because the spill of malignant cells may result in the development of metastasis.

Mitotane
Mitotane is the treatment for inoperable tumours, metastatic disease and after incomplete resection.[18] Mitotane is an isomer of the insecticide p,p'-DDD and chemically related to insecticide DDT. Its cytotoxic effect on the adrenocortical cells leads to necrosis of the fascicular and reticular zone. Metabolic activation is necessary for its adrenolytic effect. Adrenal steroidogenesis is also impaired by the inhibitory effect on steroidogenic enzymes.[19]
Mitotane is given as tablets (Lysodren). Mitotane leads to tumour regression in 27% of the patients with advanced adrenocortical carcinoma and to control of hormone excess in the majority of patients.[7] Objective tumour response was found only among patients with a mitotane level of more than 14 mg/l.[18,19]
The therapeutic plasma levels vary between 14 and 20 mg/l, measured at least 12 hours after the last ingestion with an initial measurement after 14 days. The initial dose of mitotane is 1.5 g/day, rapidly increasing to 5 to 6 g/day depending on the patient's tolerance of the drug. The dose is adjusted according to the mitotane plasma concentration and tolerability. Plasma levels above 20 mg/l can lead to serious side effects probably without enhancing the effectiveness. Possible side effects are gastrointestinal symptoms (nausea, vomiting, diarrhoea, anorexia), neurological symptoms (insomnia, confusion, depression, tremor, ataxia) and a prolonged bleeding time due to platelet dysfunction.[20] Additional side effects can occur due to adrenal insufficiency and elevated plasma steroid-binding capacity. Therefore, hydrocortisone and fludrocortisone substitution, in high doses, is necessary. The exact dose is determined by the clinical condition, blood pressure and laboratory parameters (Na, K, ACTH).[18]
After total regression, mitotane is continued for one to two years. With persisting, stable disease mitotane can be continued lifelong, or as long as considered necessary.

Chemotherapy
The choice of chemotherapy in the treatment of adrenocortical carcinoma is based on small trials (*table 1*). No prospective randomised trials are available because of the low incidence of adrenocortical carcinoma.
Berruti *et al.* showed that the combination of etoposide, doxorubicin, cisplatin and mitotane is a therapeutic option in advanced adrenocortical carcinoma.[21] Kahn *et al.* showed positive results with the streptozotocin and mitotane.[22]

INTERNATIONAL COOPERATION: TRIAL

The international consensus conference on adrenal cancer, in Ann Arbor, USA in September 2003, recommended both etoposide, doxorubicin, cisplatin in combination with mitotane, and streptozotocin in combination with mitotane as therapeutic options in advanced adrenocortical carcinoma.
As a result of this conference the Collaborative Group for Adrenocortical Cancer (COACT) has been set up. The COACT has taken the initiative to start a large

Table 1. *Overview of studies for cytotoxic chemotherapy for adrenocortical carcinoma*

Cytotoxic compound	Mitotane	n	CR (n)	PR (n)	Total (%)	Reference
I	-	12	-	-	0	18
P, E	-	45	-	5	11	19
D, V, E	+	35	1	4	14	20
C, D, P	-	11	-	2	18	21
D	-	16	1	2	19	22
D, P, 5-FU	-	13	1	2	23	23
P	+	37	1	10	30	24
P. E	+	18	3	3	33	25
S	+	22	1	7	36	26
P, E	-	13	-	6	46	27
E, D, P	+	28	2	11	54	28
		250	10	52	25	

I=irinotecan, D=doxorubicin, E=etoposide, 5-FU-5fluorouracil, C=cyclophosphamide, V=vincristine, S=streptozotocin, P=cisplatin, CR=complete response, PR=partial response.

international study: FIRM ACT (First International Randomised Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment). A multicentre cooperation is the only way to implement this trial. It is a phase III, randomised, open-label, cross-over trial, with the Netherlands, Sweden, Italy, Germany, France, United States and Australia participating. The FIRM-ACT trial compares etoposide, doxorubicin, cisplatin and mitotane (EDP/M) with streptozotocin and mitotane (Sz/M), in order to determine a standard therapy for advanced adrenocortical carcinoma (*figure 1*). The total duration of the trial will be seven years, five of which will be for trial inclusion. In total 300 patients will be randomised. The most important inclusion criteria are histologically confirmed diagnosis and a stage III-IV metastatic disease.

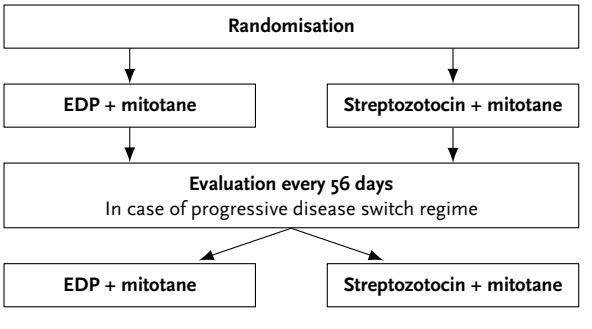
During the treatment with EPD/M, four days of chemotherapy is administered every four weeks. On the first day doxorubicin 40 mg/m^2 is administered, followed by three days of etoposide 100 mg/m^2, the last two days in combination with cisplatin 40 mg/m^2.

In the first five days of the Sz/M scheme streptozotocin 1g is administered daily, followed by 2 g/day during the next 21 days. In both groups mitotane is administered daily, with a plasma level between 14 and 20 mg/l. Mitotane is started at least two weeks before starting the other chemotherapy.

The primary endpoint is whether the EDP/M regimen prolongs overall survival compared with Sz/M. Secondary endpoints are the quality of life, time to progression, time till response and total response duration of the disease. The relation between the plasma levels of mitotane and the overall survival will be determined for both treatment groups.

In case of unacceptable toxicity or progression of the underlying disease, patients will be treated according to the treatment regime of the other group, so that second-line treatment data will become available for both treatment regimes.[23]

Figure 1. *Randomisation regimen in the Firm-ACT trial*



NATIONAL COOPERATION: THE DUTCH ADRENAL NETWORK

The Dutch Adrenal Network was set up in 2004 as a national cooperation of endocrinologists, pathologists and oncologists from all (eight) academic centres and Máxima Medical Centre in Eindhoven.

This has resulted in the combination of more knowledge and expertise and provides patients with the opportunity to receive optimal treatment in their own district. In clinical practice the Dutch Adrenal network participates in telephone consultation by local doctors, referral of patients to one of the regional centres, and referral of patients from regional centres to the trial centres (Leiden University Medical Centre (LUMC), Academic Medical Centre (AMC) and Máxima Medical Centre (MMC). In the VU University Medical Centre (VUmc) and the University Medical Centre Groningen (UMCG) the trial has been presented to the METC. The Dutch Adrenal Network also plays an important role in determining and/or modifying the treatment policy for patients with adrenal cortical carcinoma.

The Dutch Adrenal Network strives to increase knowledge of both the pathogenesis and the prognostic factors of the disease.

In early 2005, 53 patients were treated in the Network, which reflects about 50% of the total population with adrenocortical carcinoma in the Netherlands. The goal is to increase this number, so that more patients get the best possible treatment and care.

CONCLUSION

Adrenocortical carcinoma is a rare disease with a poor prognosis. Chemotherapy can be effective in patients with metastatic disease. To improve the treatment of adrenocortical carcinoma, national and international cooperative alliances have been set up. International cooperation has resulted in a randomised trial aimed at determining a standard therapy for advanced adrenocortical carcinoma. The Dutch Adrenal Network is a national cooperation with the primary goal to give patients the best possible treatment, by bringing together knowledge and expertise, and trying to implement this regionally.

APPENDIX 1

The Dutch Adrenal Network
Radboud UMC Nijmegen: Prof. Dr. A.R.M.M. Hermus
UMCG Groningen: Prof. Dr. B.H.R. Wolffenbuttel
AMC Amsterdam: Dr. J.H. de Vries, Dr. J.W. Wilmink
LUMC Leiden: Prof. Dr. J.A. Romijn, Dr. A.J. Gelderblom
VUmc Amsterdam: Dr. M. Eekhoff

AZM Maastricht: Dr. N.C. Schaper, Dr. A.P. de Bruine
UMCU Utrecht: Dr. P.M.J. Zelissen
Erasmus MC, Rotterdam: Dr. W.W. de Herder, Dr. R.R. de Krijger
MMC Eindhoven: Dr. M.W. Dercksen

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REVIEW

Incretins: a new treatment option for type 2 diabetes?

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ABSTRACT

This article describes how the discovery of a protein almost 100 years ago led to a clinical treatment for type 2 diabetes. Food intake, but also stimulation of the sympathetic nervous system (for example physical exercise), stimulates the secretion of glucagon-like-peptide-1 (GLP-1), derived from the glucagon precursor proglucagon in the small intestine. GLP-1 stimulates the production and secretion of insulin, the release of somatostatin, glucose utilisation by increasing insulin sensitivity and in animal studies also β-cell function and expansion (proliferation). It inhibits glucagon release, gastric emptying, appetite and food intake via the central nervous system and in animal experiments also apoptosis of β-cells.

Since GLP-1 has to be administered parenterally and its half-life is short, a long-acting GLP-1 receptor agonist (exenatide) and a long-acting GLP-1 analogue (liraglutide) have been developed as well as an inhibitor of DPP-IV (the enzyme that breaks down endogenous GLP-1). Clinical studies with exenatide and liraglutide as monotherapy show a significant increase in the postprandial insulin concentration as well as a smaller increase in the postprandial glucose values. Adding these drugs to standard oral glucose-lowering medication shows improvement in glucose and insulin concentrations and HbA_{1c} compared with adding placebo. The effect of exenatide on HbA_{1c} is the same as adding a long-acting insulin analogue (glargine), but the increase in weight after adding insulin is not seen after exenatide, where even a small decrease in weight is found. This is an important advantage, because most type 2 patients are already obese. Whether less β-cell apoptosis and maintenance of β-cell function occurs, as has been shown in animal studies, has to be awaited.

Clinical studies with the oral DPPIV inhibitors sitagliptin and vildagliptin show promising results, but are only published as abstracts at scientific meetings.

KEYWORDS

Incretins, GLP-1 analogues, GLP-receptor agonist, DPP-4 inhibitors

INTRODUCTION

The treatment of type 2 diabetes mellitus includes correction of both insulin resistance and impaired insulin secretion. Therefore, besides lifestyle intervention, treatment consists of medical therapy with drugs that lower insulin resistance such as metformin and thiazolidinediones (TZDs) but also insulin secretaguoges (or insulin). Although hyperinsulinaemia is a hallmark of the first years after diagnosis, the first-phase insulin response (peak after a glucose load) is impaired or absent early in the disease. This first-phase insulin response is caused by a peptide from the small intestine secreted after an oral glucose load. As early as in 1906, Moore discovered a chemical stimulant for the pancreas produced by the duodenum. In 1930, Labarre introduced the term 'incretin'. McIntyre *et al.* were the first to demonstrate an incretin effect in 1964. In 1969 Brown *et al.* isolated the protein and called it gastric inhibitory peptide. In 1982 Lund *et al.* identified the cDNA for preproglucagon. In 1983 Bell *et al.* cloned human cDNA for preproglucagon from which glucagon-like-peptide-1 and GLP-2 are a part. In 1987 Kreymann *et al.* demonstrated that GLP-1 indeed stimulates insulin-secretion in humans.[1]

THE ENTEROINSULINAR AXIS: INCRETINS

Glucose-dependent insulinotropic polypeptide (GIP) and GLP-I are the two most important incretins produced by the duodenum. The hypothalamus also produces an incretin, pituitary adenylate cyclase-activating peptide

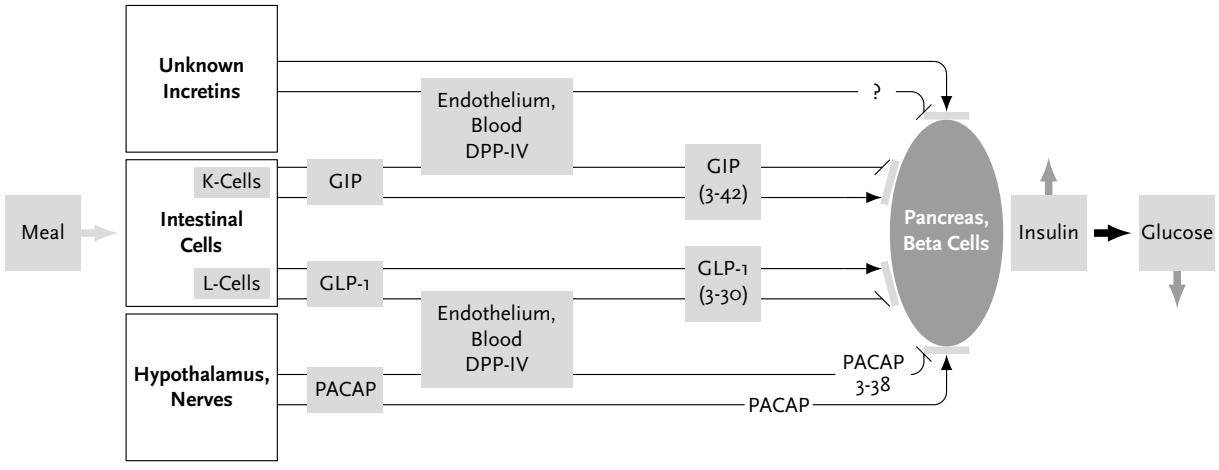
(PACAP); the exact contribution of this peptide to insulin secretion is not clear yet. GIP induces ±60% of the incretin effect. *Figure 1* shows the enteroinsulinar axis: the uptake of carbohydrates and amino acids in the gut results in an endocrine response in the islets of Langerhans. It also causes neurotransmission to both the islets, the liver and via the nuclei of the medulla oblongata to the hypothalamus. Efferent neurons from the hypothalamus and medulla oblongata activate the vagus nerve and the pancreas and inhibit the gastrointestinal tract.[2,3] The endogenous secretion of GIP in type 2 diabetes is normal and exogenous administration of GIP does not increase the insulin response. The endogenous secretion of GLP-1 in type 2 diabetes, however, is decreased. Exogenous administration does induce insulin secretion.[4]

GLP-1 is predominantly produced in the small intestine. After intake of carbohydrates a sixfold increase in the plasma concentration is observed. The time of action is only a few minutes. It is cleared from the plasma by the liver and the kidney.[5] The effect of GLP-1 on different tissues is shown in *table 1*. GLP-1 stimulates insulin production and insulin release after food intake, somatostatin release, glucose uptake by increasing insulin sensitivity and in animal models also β-cell function and expansion (proliferation). It inhibits glucagon release, gastric emptying, appetite and food intake via the central nervous system and also apoptosis of the β-cells. It also influences body temperature, energy expenditure, fluid and salt retention and release of pituitary hormones.[6-8] Administration of GLP-1 to people with type 2 diabetes lowers both fasting and postprandial glucose and decreases appetite and food intake.[9,10] Probably indirectly, as a result of reduced intake of free fatty acids and glucose, insulin sensitivity and β-cell function increase (less glucose toxicity). GLP-1 has to be administered parenterally and has a short half-life, which makes it unsuitable for daily use. Therefore, GLP-1 analogues have been developed with a longer half-life by making natural GLP-1 resistant to the degrading enzyme dipeptidyl peptidase IV (DPP IV), which made twice daily subcutaneous dosing possible. Also a GLP-1 receptor agonist has been developed (exenatide) with a GLP-1-like action. Finally, drugs that increase endogenous GLP-1 by inhibiting DPP-IV, the enzyme responsible for degradation of GLP-1, are becoming available.

Table 1. *Effects van GLP-I on several tissues*

Tissue	Effect
Stomach	Delays gastric emptying
Small intestine	Slows gut motility
Liver	Stimulates glycogen synthesis
Fat	Stimulates glycogen synthesis Inhibits lipogenesis
Skeletal muscle	Stimulates glycogen synthesis
Exocrine pancreas	Inhibits enzym release
Endocrine pancreas	Stimulates insulin release Stimulates somatostatin release Stimulates Beta-cel neogenesis Stimulates synthesis of proinsulin Inhibits glucagon synthesis Inhibits apoptosis of Beta-cells
Central nervus system	Inhibits food intake Stimulates satiety Increases body temperature Stimulates TSH, LH and vasopressin secretion
Kidney	Stimulates sodium excretion Inhibits H+ excretion Inhibits glomerular hyperfiltration
Heart	Increases blood pressure Increases heart rate

Figure 1. *Schematic overview of the production and action of the incretines: GIP, GLP-I and PACAP on the Beta-cel. DPP-IV inhibitors inhibit the degradation of these incretines.*



GIP = Gastric Inhibitory Peptide; GLP-I = Glucagon-Like Peptide-I; PACAP = Pituitary Adenyl-Cyclase-Activating Peptide.

CLINICAL STUDIES

Exenatide

As is often seen in medicine, exenatide was discovered more or less by chance. The peptide from the saliva of the Gila monster happened to be homologous with GLP-1 for 53%, showed more affinity for the GLP-1 receptor than GLP-1 itself and was DDP IV resistant. It enhances insulin secretion, delays gastric emptying and lessens food intake. The plasma half-life is three to four hours.[9] Clinical studies show both effects on glucose regulation, body weight and lipid parameters.

Studies with exenatide as add-on therapy with oral hypoglycaemic drugs

Exenatide has been added to either sulphonylurea,[12-14] metformin, or a combination of both in people with type 2 diabetes and HbA_{1c} >7% on this medication only. The glycaemic result after 30 weeks was similar in all studies and showed a significant decrease in both fasting and postprandial glucose and a change in HbA_{1c} of -0.8% compared with +0.1% with placebo. In the first study, HbA_{1c} decreased significantly in comparison with placebo (slight increase) and even more with exenatide 10 μg subcutaneously twice daily. Starting with a mean HbA_{1c} of 8.6%, 41% of patients reached an HbA_{1c} of <7% after 30 weeks. There was a significant decrease in body weight of 1.6 kg after 30 weeks. Extension studies of two years show that the favourable effects on fasting glucose and HbA_{1c} are sustained.[15-17] Among patients who completed the 82 weeks of treatment, mean body weight further decreased from −2.1 kg at 30 weeks to −4.4 kg at 82 weeks, respectively.
Exenatide BID has recently been reported to have favourable effects as add-on therapy with TZDs and with combination therapy of TZD+metformin.[18]

Studies comparing exenatide with insulin/as add-on therapy with insulin

In two studies[19,20] exenatide was compared with insulin glargine once daily added to the same oral glucose-lowering drugs over a period of 26 weeks. The dose of glargine was titrated to reach a fasting glucose of 5 mmol/l. A similar reduction in HbA_{1c} of -1.1% was achieved. The fasting glucose was significantly lower in the glargine-treated patients, whereas exenatide provided significantly lower postprandial blood glucose values. The fluctuation in blood glucose values was significantly less with exenatide than with insulin glargine. Given the epidemiological data that lower postprandial glucose values are more important than fasting glucose in reducing the risks of cardiovascular disease this may contribute more to reduction of CVD risks than is indicated by the reduction in HbA_{1c}. The group treated with glargine showed an increase in body weight of 1.8 kg, whereas in the group treated with exenatide a weight loss of 2.3 kg was seen. Hypoglycaemia at night was significantly more often seen in the group treated with glargine. Hood evaluated the use of exenatide in patients with type 2 diabetes using insulin and/or oral hypoglycaemic drugs with an HbA_{1c} ≤7.0%.[21] The patients using an insulin secretagogue were able to discontinue its use, and the patients using insulin could reduce the mean daily dose by -37% and the number of injections by -39%. The average weight loss in the 3.6 months was -5 kg compared with a weight gain of +4.8 kg in the preceding 2 years.
Post-hoc interim analyses of the 82-week completer cohort[20] showed a significant 12% increase in HDL cholesterol, a 16% lowering of triglycerides and 3% lowering of diastolic blood pressure. Total cholesterol, LDL-C, apolipoprotein B and systolic blood pressure did not improve significantly.

Exenatide was approved by the FDA as an adjunctive treatment for type 2 diabetes in patients unable to achieve adequate control using metformin and/or sulphonylurea therapy. In Europe the EMEA gave similar approval.
A slow-release preparation (LAR) for once-weekly subcutaneous administration has been tested in rats. A phase II exenatide LAR clinical trial in 45 patients with type 2 diabetes treated with metformin or diet and exercise showed promising results.[22]
Effects on increase in β-cell mass, as demonstrated in animal models, can only be shown with surrogate markers like durability of glycaemic control in humans. Long-term controlled clinical trials addressing this issue are currently being performed.

LIRAGLUTIDE

Liraglutide is a long-acting GLP-1 analogue that is 97% homologous to GLP-1, which makes it suitable for once-daily subcutaneous injection. Acylating the peptide with a free fatty acid chain improves binding to albumin, makes it less accessible to DPP-IV and inhibits renal filtration. Also the binding to albumin induces a slower resorption from the place of injection. Animal studies have shown that liraglutide decreases plasma glucose levels, increases insulin secretion, reduces glucagon secretion, inhibits gastric emptying and appetite, resulting in a reduced body weight and increased β-cell volume.[10]
Phase I studies in humans have been performed, while phase II studies have been completed[23-28] or are ongoing. Hypoglycaemia is seldom reported with liraglutide as monotherapy. Dose-titration studies investigated doses of up to 2 mg/day. In the five-week study by Nauck *et al.*[27] liraglutide added to metformin monotherapy reduced fasting glucose by -3.9 mmol/l and HbA_{1c} by 1.2%. Liraglutide in combination with metformin was significantly more effective than metformin combined

with glimeperide. Body weight was significantly lower in the metformin and liraglutide group *vs* metformin with glimeperide. Frequently reported side effects were nausea, vomiting and diarrhoea as with all GLP-1-like drugs, but adverse events were mild, transient and rarely caused discontinuation of liraglutide treatment.

DPP-IV INHIBITORS

Although studies in healthy volunteers show that administration of DPP-IV inhibitors alone decreases endogenous GLP-1 production, the administration of DPP-IV inhibitors induces a doubling of endogenous GLP-1 production and increases the ratio of active/total GLP-1 making a physiological insulin secretion possible in people with type 2 diabetes.[14] The DPP-IV inhibitors also increase the physiological effects of other incretins such as gastric inhibitory peptide and PACAP. The exact consequences of these additional effects are still not known. The possible advantage of DPP-IV inhibitors in comparison with GLP-1 analogues is that they cause little delay in gastric emptying, which might diminish gastrointestinal side effects. However, the effect is less powerful than that of LP-1, GLP-1-receptor agonists or GLP analogues and starts later (after a few weeks).

Twelve-week monotherapy with vildagliptin improves HbA_{1c} in patients with type 2 diabetes. The higher the baseline HbA_{1c}, the more the effect.[29] Vildagliptin at a dose of 100 mg for 4 weeks reduced fasting and postprandial glucose concentrations, as well as plasma glucagon levels, while the ratio of insulin to glucose increased.[30] Adding vildagliptin to metformin in patients with type 2 diabetes resulted in a decrease in HbA_{1c} of 0.8% after 12 weeks compared with placebo. This difference was maintained in a 52-week extension study.[31] Insulin secretion, measured by a postmeal area under the 0-30 min C-peptide curve, was increased in the vildagliptin group compared with metformin alone. Insulin sensitivity during meal ingestion also increased in the vildagliptin-treated patients.[32]

Clinical studies with sitagliptin and presentations at the American Diabetes Association and International Diabetes Federation meetings in June and December 2006, respectively, indicated that sitagliptin is well tolerated and effective in both monotherapy and in combination with metformin or pioglitazone without significant hypoglycaemia or weight gain.[33-35]

CONCLUSION

The development of GLP-1 analogues, GLP-receptor agonists and DPP-IV inhibitors offers new possibilities for the treatment of hyperglycaemia in people with type 2 diabetes. Although the pathophysiological processes in time and the natural history of type 2 diabetes are not quite clear, it is evident that both insulin secretion and insulin action are impaired at the start of the disease. Especially the first-phase insulin response is absent. In theory this would imply that treatment with GLP-1 analogues or receptor agonists with or without DPP-IV inhibitors in the early phase of the disease in combination with a drug that reduces insulin resistance, such as metformin and thiazolidinediones, is the most physiological treatment option. There is evidence, however, that these drugs are still effective further in the course of the disease when standard treatment is no longer effective. One of the most promising results of this new class of drugs is the absence of increase in weight and even weight reduction instead of the increase in weight often seen with the use of insulin secretagogues as sulphonylurea and insulin. Of course, results of long-term studies have to be awaited concerning both long-term efficacy and safety. However, if positive, the use of sulphonylurea derivatives, especially because of their possible adverse events in case of myocardial ischaemia, could become obsolete and insulin therapy only reserved for patients with absolute insulin deficiency.

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ORIGINAL ARTICLE

Glycaemic control, health status and treatment satisfaction with continuous intraperitoneal insulin infusion

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ABSTRACT

Background: Continuous intraperitoneal insulin infusion (CIPII) has been in use for over 20 years. High costs and technical problems have prevented its widespread use. In the Netherlands, the Isala Clinics in Zwolle is the centre with the most extensive experience with CIPII. Its use is aimed at improving glycaemic control with less hypoglycaemic events, and thus improving quality of life in patients with poorly controlled diabetes despite intensified insulin treatment. Our aim was to assess glycaemic control, health status and treatment satisfaction in subjects treated with CIPII within the Isala Clinics.

Methods: Retrospective longitudinal analysis of clinical data in 48 patients started on CIPII between 1983 and 2005. HbA_{1c} at baseline, after one year, and at present assessment or at the end of pump use were applicable. Cross-sectional assessment of health status, well-being and treatment satisfaction was carried out.

Results: Of 48 patients, 33 were treated with CIPII at the moment of assessment. Five patients died whilst on CIPII; four from diabetes-related causes, none from hypoglycaemia. HbA_{1c} decreased significantly from 9.7 to 8.8% after one year, to 8.6% at long-term follow-up; $p<0.01$. Less hypoglycaemic events were reported. Short-Form 12-Item Health Survey (SF-12) scores were 37.4 and 47.2 (range 0-100), the Well-Being Index (WHO-5) score was 52.7 (range 0-100) and median treatment satisfaction score was 32 (range 0-36).

Conclusion: CIPII leads to improved glycaemic control with less self-reported hypoglycaemic events in patients with poorly controlled diabetes. Treatment satisfaction is high. Mental health status and well-being scores are low, however.

KEYWORDS

Diabetes mellitus, intensive insulin treatment, CIPII, quality of life

INTRODUCTION

Continuous intraperitoneal insulin infusion (CIPII) has been a promising treatment for diabetes mellitus for the last 20 years. The use of the peritoneal cavity rather than subcutaneous tissue for insulin administration may explain the beneficial effect on diabetes control and the lower risk of hypoglycaemia from this treatment modality. Insulin delivered through the intraperitoneal (IP) route is better absorbed and allows blood glucose values to return to baseline values more rapidly with more predictable insulin profiles compared with subcutaneous injections of regular or long-acting insulin.[1,2] Furthermore, much of the IP insulin is absorbed by the portal system, mimicking the physiological situation and resulting in higher hepatic uptake and thus lower peripheral plasma insulin concentrations compared with systemic administration.[3] Other possible effects include improvement of the impaired glucagon secretion and hepatic glucose production in response to hypoglycaemia through alleviation of peripheral hyperinsulinaemia.[4] These properties may have a favourable impact on hypoglycaemia, thus being of importance in diminishing risk in subjects experiencing hypoglycaemia unawareness.

Research with IP delivery of insulin in type 1 and type 2 diabetic subjects has shown that it is an appropriate therapy that allows subjects to achieve acceptable glycaemic control without increasing the inherent risk of severe

hypoglycaemia observed when intensive insulin treatment is pursued.[5-10]

Living with diabetes has a major effect on health-related quality of life and well-being, not only because it is a chronic disease but also because diabetes-related tasks have to be performed every day.[11] Partly because of this, almost one in three people with diabetes suffer from symptoms of depression.[12] This and other psychosocial factors are often stronger predictors of medical outcomes such as hospitalisation and mortality than are measures such as HbA_{1c} or body mass index (BMI).[13]
It is hypothesised that CIPII can have a positive influence on quality of life, not only because it can result in better glycaemic control and less hypoglycaemic events, but also because it does not require multiple injections as does subcutaneous insulin delivery by pen, and it does not have the inconvenience of an external pump as is the case with subcutaneous insulin infusion (CSII). Results from clinical trials suggest that CIPII can indeed have a positive effect on health-related quality of life and well-being.[7-9]
Such effects provide the arguments to make IP insulin in theory the most effective and physiological mode of insulin delivery. However, due to technical problems and its high costs it is still not widely used. At this moment the only available implantable pump is the model 2007 from Medtronic/Minimed (Northridge, CA, USA), and though the CE mark approval enables commercial distribution in Europe, there is still no approval by the American Food and Drug Administration.
In the past, system blockades through insulin aggregates and catheter obstructions were the two major problems resulting in underdelivery of insulin.[10,14-15] Due to improvements in the process of preparing the specific insulin used for IP therapy, the occurrence of insulin aggregates has dropped in the recent years.[16]
Haardt *et al.* compared CIPII with multiple subcutaneous injections and reported the direct costs of CIPII as being 2.6 fold higher.[9] These data are from a decade ago, and since then improvements such as longer battery life will probably have reduced costs.

Up until 2001 approximately 1100 pumps were used worldwide, most of them in France.[14] In 2004, 406 patients were treated with CIPII.[17] In the Netherlands CIPII is only considered as a last resort for patients with 'brittle' diabetes who are not responding on multiple daily insulin injections (MDI) or CSII, or in patients with subcutaneous insulin resistance.[18]
The Isala Clinics in Zwolle is the Dutch centre with the most extensive experience with this treatment option. The objective of this report is to describe CIPII regarding glycaemic control, health status and patient satisfaction in this group of patients.

MATERIAL AND METHODS

All patients treated with CIPII and cared for in the Isala Clinics in Zwolle were eligible for the study. Data were collected on glycaemic control, duration of diabetes and data on start and cessation of CIPII from hospital records. Glycaemic control was assessed using HbA_{1c} prior to implantation, one year after implantation and at long-term follow-up.
Patients currently on CIPII and treated in our clinic received a questionnaire by mail. This survey contained questions regarding number of hospital admissions in the previous year, number of self-controls of blood glucose daily, number of hypoglycaemic events in the last four weeks and macrovascular complications. BMI was calculated with self-reported height and weight for all survey respondents and in other cases data from hospital records were used. In addition, we asked about perception regarding glycaemic control and hypoglycaemic events with CIPII as compared with previous insulin treatment. Finally, using self-administered questionnaires, health status and treatment satisfaction were assessed.

Health status, well-being and treatment satisfaction

To measure health status and well-being the Short-Form 12-Item Health Survey (SF-12) and the WHO-5 Well-Being Index (WHO-5) were used.[19,20]
The SF-12 is a generic measure of health status and is derived from the Short-Form 36-Item Health Survey (SF-36). Using scoring algorithms two summary scores can be derived from the SF-12: the Mental Component Summary (MCS) and the Physical Component Summary (PCS).[21] These summary measures are highly correlated with the SF-36 summary measures.[19] Gandek *et al.* reported on the high degree of equivalence observed in ten countries (including the Netherlands) and therefore recommend using the standard scoring algorithms. The PCS and MCS scores have a range of 0 to 100 and were designed to have a mean score of 50 and a standard deviation of 10 in a representative sample of the US population.[22] The SF-12 has been found to be both valid and reliable. Both the SF-36 and the SF-12 are widely used health status measurement tools. This makes comparison of health status of different populations possible.

The WHO-5 is derived from a larger rating scale developed for a World Health Organisation project on quality of life in primary health care.[20] It was designed to measure positive well-being. The WHO-5 is recommended by the WHO as a first step in a two-stage screening process for depression.[20] The WHO-5 consists of five items, whereby every answer is given on a score between 0 and 5, giving a raw score from 0 to 25. To allow comparison with other

scales, the WHO-5 can be transformed to a 0 to 100 scale. A raw score below 13, i.e. score below 50 on the 0 to 100 scale, indicates poor well-being and is considered to be an indicator for depression, which should be confirmed using the Major (ICD-10) Depression Inventory and patient interviews.[23] High reliability and clinical validity of the WHO-5 as a screening instrument of depression and well-being in people with diabetes was found by Shea *et al*.[24]

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to measure satisfaction with treatment.[25] The DTSQ can be applied for both type 1 and type 2 diabetes patients. The questionnaire consists of eight items, all scored on a seven-point scale, ranging from 'very satisfied' (6) to 'very dissatisfied' (0). The DTSQ has three subscales: treatment satisfaction (6 items), perceived frequency of hyperglycaemia (1 item) and perceived frequency of hypoglycaemia (1 item).[25] The DTSQ has been used in Dutch studies.[26,27]

Statistical analysis

The statistical analyses were carried out using SPSS version 12.0.1. Statistical significance was taken at $p<0.05$. Where appropriate, parametric (Student's t) and non-parametric (Mann-Whitney U) tests were used to compare outcome measures. To test the difference in HbA_{1c} and BMI paired samples t-tests were performed.

RESULTS

Forty-eight patients were identified who had received an implantable insulin pump for CIPII in the Isala Clinics in Zwolle, the Netherlands from 1983 up till December 2005. At the time of our study in December 2005, 33 patients were treated with CIPII. Patient characteristics are shown in *table 1*.

Reasons for cessation of CIPII are given in *table 2*. In total 33% (n=5) died while on CIPII, in four cases the cause of death was diabetes related, with kidney failure and heart failure each being the cause of death in two cases. Since cessation of CIPII, four patients died while on other forms of insulin therapy.

The response of patients still on CIPII regarding the questionnaire was high with 30 out of 33 (91%) questionnaires returned.

Glycaemic control

HbA_{1c} at all three study points could be retrieved for 41 out of 48 patients. Patients reported less hypoglycaemic events with CIPII. Mean HbA_{1c} before implantation was 9.7% (SD 1.7). One year after implantation (median 12.0 months, P^{25}-P^{75}: 9.5-14.0) HbA_{1c} had decreased significantly to 8.8% (SD 1.7) ($p=0.004$). This improvement was sustained during long-term follow-up: HbA_{1c} at follow-up after a mean of 6.0 years (median 4.5; P^{25}-P^{75}: 2.3-11.1) was 8.6% (SD 1.6) ($p=0.001$ *vs* baseline).

Table 1. *Patient characteristics*

Characteristic	All patients	Currently on CIPII [1]
n	48	33
Sex (m/f) (*n*)	10/38	7/26
Type of DM (*n*)		
1	41	27
2	6	6
Undetermined	1	-
Age at time of implantation (years)	36.3 (13.1; 13.8 – 60.6)	36.6 (14.4; 13.8 – 60.6)
Diabetes duration at time of implantation (yrs)	17.2 (9.8; 3 – 37)	16.3 (9.1; 3 – 37)
HbA_{1c} (%)	9.7 (1.7; 6.1 – 12.6)[2]	9.9 (1.5; 7.2 – 12.0)[2]
Smoking (%)	25	27
Use of alcohol (%)	49	49

Values are number of patients, mean (SD; range) or percentage of patients; [1]at assessment in fourth quarter of 2005; [2]missing data due to incomplete dataset; DM= diabetes mellitus.

Table 2. *Cessation of CIPII*

Reason for stopping CIPII *	n
Inadequate glycaemic control	4
Pump failure	3
Kidney/pancreas transplantation	2
Recurrent infection of pump	1
Death from diabetes related complications	
Kidney failure	2
Heart failure	2
Death from other cause	1

*** as recorded in hospital records.**

BMI

BMI could be calculated both before and on CIPII for 26 patients. Mean BMI did not increase significantly: 24.4 (SD 4.0) before CIPII to 25.1 (SD 4.3) on CIPII ($p=0.46$; median 3.5 years after implantation, P^{25}-P^{75}: 1.9-12.9).

Self-reported variables

The self-reported variables are shown in *table 3*. Altogether, 73% reported no hospital admissions related to their diabetes in the year preceding the questionnaire. The median number of daily blood glucose measurements was 5 (P^{25}-P^{75}: 4-7). Some 87% perceived a better glycaemic regulation on CIPII as compared with previous insulin treatment modalities, while 67% perceived less hypoglycaemic incidents with CIPII.

Table 3. *Patient reporting on hospital admission, self-control of blood glucose, macrovascular complications, glycaemic control and hypoglycaemic events*

Variable	N	Variable	n
Number of hospital admissions in last year		Self-control of blood glucose (times/day)	
Diabetes related			
0	22	1-5	14
1	3	5-10	14
2-4	3	>10	1
≥5	2	Not recorded	1
Non-diabetes related		Macrovascular complications	
0	20	Yes	7
1	5	No	20
2-4	4	Do not know	2
≥5	1	Not recorded	1
Day time hypoglycaemic events (n/4 weeks)		Night time hypoglycaemic events (n/4 weeks)	
0	5	0	16
1-5	9	1-5	10
5-10	10	5-10	1
≥10	5	≥10	1
Not recorded	1	Not recorded	2
Perceived better glycaemic control with CIPII		Perceived less hypoglycaemic events with CIPII	
Yes	26	Yes	20
No	1	No	1
No difference	2	No difference	8
Not recorded	1	Not recorded	1

One or more macrovascular complications (myocardial infarction, angina, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), stroke or intermittent claudication) were reported by 23% (n=7); 47% (n=14) reported having hypertension.

Health status and patient satisfaction

Due to missing answers, the SF-12 scores of two out of 30 patients could not be calculated. SF-12 PCS was 37.4 (SD 12.1) and SF-12 MCS was 47.2 (SD 11.1). Mean score on the WHO-5 was 52.7 (SD 28.6) (n=30). Median score for treatment satisfaction was 32 (P^{25}-P^{75}: 28-36; n=28). There where no differences between men and woman regarding scores on SF-12, WHO-5 or DTSQ (p>0.1).

DISCUSSION

With this present study we report details regarding a population of Dutch patients with diabetes mellitus treated with CIPII and cared for in a single centre in the Netherlands. Data were assessed regarding glycaemic control, health status, well-being and treatment satisfaction.

Most available research on CIPII was conducted in either France or the US. Up till now no prospective randomised trials with CIPII have been performed in the Netherlands.

Our results concerning glycaemic control and quality of life are consistent with the results presented by De Vries *et al*. in 2002, who studied part of the population presented in this article. Twenty of 33 patients in their analysis were treated in our hospital at that time.[18] Our report provides further evidence on the long-term efficacy of CIPII regarding glycaemic control and hospital admissions with a mean follow up of 6.0 years. In addition to De Vries *et al.* we now report on treatment satisfaction and well-being.

Our results regarding current health status of patients with diabetes mellitus treated with CIPII are comparable with the health status of patients with diabetes mellitus and comorbidity as reported by Rijken *et al.*[28] Compared with the general Dutch population as reported by Gandek *et al.* the SF-12 MCS of our population is lower.[22]

The mean score on the WHO-5 in our population is much lower than the mean score of around 70 in the general population.[23] The cut-off point for further testing for depression is a score below 50 (raw score below 13). When applying this cut-off point to our data, 39% of our population have an indication for further testing (n=13). The percentage of patients scoring below the cut-off point on the WHO-5 is higher in our population then the percentages reported by Rakovac *et al*. for patients with type 1 and type 2 diabetes, 23 and 30.9% respectively.[29] However, due to the small population size in our study, this difference may be based solely on a sampling error.

The high level of satisfaction with treatment in our study is comparable with the treatment satisfaction levels reported for CSII and MDI by Hoogma *et al.*[27] Home *et al*. reported baseline treatment satisfaction levels of patients with type 1 diabetes mellitus in their randomised controlled trial comparing insulin aspart with human insulin that are also similar to our levels.[30] Although ceiling effects of the questionnaire used have been raised as a point of concern,[31] this will pose less of a problem in a cross-

sectional measurement.[32] To assess future satisfaction, use of the 'Change version' of the questionnaire might be appropriate.[32]

Based on these data we conclude that although treatment satisfaction with CIPII is high and very similar to treatment satisfaction of type 1 diabetes mellitus patients on MDI or CSII, mental health status and well-being of this population are lower than for other treatment modalities. We can only hypothesise about the determinants of these low scores. There is some evidence for the association of duration of diabetes and being female with decreased quality of life, which may partly explain the results found in our study.[33] Mean duration of diabetes at the time of the study was almost 25 years and the percentage of females almost 80%. We do not have the full data on the nature and occurrence of physical symptoms and microvascular complications in our population; these complications will have a negative impact on well-being and health status.[34] Furthermore, we do not know the coping behaviours and personality characteristics of our patients, parameters known to influence quality of life.[35]

Study limitations

The retrospective design is the main limitation of our study. Data on hospital admissions and macrovascular disease were based on self-reporting and this could potentially be a study limitation. Furthermore, we do not have baseline scores for health status, well-being and treatment satisfaction.

CONCLUSION

In conclusion, based on our data, CIPII does improve glycaemic control without increasing the risk of hypoglycaemic events. Furthermore, treatment satisfaction with CIPII is high and in the same range as treatment satisfaction with other intensive treatment modalities. Mental health status and well-being of the patients studied were low, with further investigation regarding depression probably being appropriate in one out of three patients.

To date, CIPII is still a last-resort treatment in the Netherlands. Most patients are concentrated in one clinic. The consequence is that eligible patients sometimes have to travel great distances for evaluation, implantation, refilling and emergencies concerning CIPII. Data on the performance of CIPII in France suggest that CIPII would be an effective treatment option for more patients with diabetes mellitus. Almost all the evidence we have on CIPII comes from French or American studies on the subject. We think there is a need for evidence from other countries where this treatment modality is used.

At this moment, a randomised cross-over clinical trial is being conducted in our centre to provide information about the safety and efficacy of CIPII in patients with diabetes mellitus type 1 and poor glycaemic control. Results of that study will help to answer the question whether CIPII is a safe and effective treatment option for diabetes mellitus.

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ORIGINAL ARTICLE

Follow-up for osteoporosis in older patients three years after a fracture

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ABSTRACT

Background: Recently a Fracture and Osteoporosis outpatient clinic (FO clinic) was set up at the University Medical Centre Groningen (UMCG) with the aim to optimise case-finding of osteoporosis in older patients with a low-energy fracture. To provide a diagnostic setting before the start of our FO clinic, case-finding was carried out in patients who suffered an 'osteoporotic' fracture in the year prior to the foundation of the FO clinic. During a three years follow up project, osteoporotic patients who needed therapy were identified.

Methods: Patients aged ≥50 years who were seen in the UMCG for a low-energy fracture (shoulder, wrist or hip) one year before that period were asked to participate. The study was carried out in two parts – a telephone questionnaire and measurement of the bone mineral density (BMD). The data were compared with the results of the FO clinic.

Results: Of the 191 patients, 88 could be contacted and were analysed. Of these 88 patients only 12 had undergone additional investigations for the presence of osteoporosis in the year of the fracture, and only six patients were on antiosteoporosis medication; 45 patients had already suffered an earlier fracture and ten had a more recent subsequent fracture. Measurements three years after their fracture revealed that 55% of the 88 patients had osteoporosis (T-score less than -2.5 SD).

Conclusion: After a fracture, case-finding for osteoporosis is good clinical practice. In our study more than half of the patients were lost for follow-up after three years. But it is still worthwhile to check whether patients with fractures in the past had the necessary diagnostics and proper therapy. Comparing these results with those of the FO clinic, it is evident, however, that case-finding of osteoporosis after a fracture can be organised most effectively at the location where the patient first attends for treatment of the fracture, namely in the emergency department of the hospital.

KEYWORDS

Osteoporosis, fracture, low energy, outpatient clinic, older patients

INTRODUCTION

Osteoporosis is a systemic skeletal disease, characterised by low bone mass and a microarchitectural deterioration of bone tissue, leading to an increase in bone fragility and susceptibility to fracture.[1] The disorder often remains unnoticed up to the moment that a fracture occurs. Fractures of the hip, vertebrae and wrist are the most commonly occurring 'osteoporotic' fractures in the Netherlands and account for more than half of the total number of these fractures, estimated at more than 80,000 per year.[2,3] Fractures in bones affected by osteoporosis form a major health problem given the significant morbidity and mortality rates and the high socioeconomic costs.[2,4,5] Treatment costs are currently estimated to be more than € 300 million a year.

In our country we have guidelines for the prevention, diagnosis and treatment of osteoporosis. The Second Revised Guideline on Osteoporosis from the Dutch Institute for Healthcare Improvement, CBO, was published in 2002.[1,6] The recommendation was made that additional investigations should take place for patients with clear risk factors for osteoporosis, described in the guidelines as case-finding. Despite the existence of guidelines, including international ones, investigation for osteoporosis in older patients suffering from a fracture as a result of a low-energy injury does not always take place. The percentage of patients sustaining an osteoporotic fracture that are investigated for the presence of, or receive treatment for, osteoporosis currently varies between 10 and 25%.[7-9] In large clinical trials it has been proven that suitable medication can reduce the risk of a subsequent fracture by

more than half.[10-12] This underlines even more the necessity to look actively for osteoporosis.

A Fracture and Osteoporosis outpatient clinic (FO clinic) was set up at the University Medical Centre Groningen (UMCG) in 2003 in response to the above-mentioned CBO guideline with the aim to optimise case-finding of osteoporosis in patients aged ≥50 years with a fracture.

In order to determine to what extent case-finding of osteoporosis took place before the establishment of this FO clinic, all patients aged ≥50 years, who visited the Emergency Department of the UMCG the year before because of a low-energy fracture of the humerus, wrist or hip, were invited to take part in this investigation for the presence and treatment of osteoporosis. The aim of this study is to make an inventory of the fracture history and other risk factors and to analyse the extent of first-line case-finding and treatment of osteoporosis in the pre-FO era and the following three years. Bone mineral density (BMD) was determined three years after follow-up and treatment was started if necessary. Data were also compared with the first results from the FO clinic, as published in the *Nederlands Tijdschrift voor Geneeskunde*.[13]

MATERIALS AND METHODS

Patients aged ≥50 years who were treated in the UMCG in 2001 for a subcapital humeral, distal radial or intracapsular hip fracture (= the index fractures) as a result of a low-energy injury were identified in the trauma database of the UMCG using the International Classification of Diseases (ICD9 codes 8134*, 8120* and 8200*/82020/82080). Data concerning the type of fracture and the treatment given were obtained from the medical file.

The study was carried out in two parts – a questionnaire by telephone and a BMD measurement by means of dual energy X-ray absorptiometry (DEXA). The questionnaire included questions about the nature and circumstances of the accident and presence of relevant risk factors for osteoporosis as mentioned in the CBO guideline (*table 2*). The questionnaire also asked whether the fracture had resulted in an investigation of any possible underlying causes, who had taken the initiative for any such investigation and whether this was followed by further treatment.

A total of 273 patients were identified. At the time of the study (October 2003 – June 2004) 191 patients could be contacted by means of a written invitation to take part in the study (45 patients had died, 5 could not be traced, 5 lived outside the region and 27 did not react to the invitation). Of these 191 patients, 103 declined to take part in the study for a variety of reasons: no interest (38), already being treated for osteoporosis (12), in too poor a physical condition (35) or other reasons (18). Eventually, it was possible to carry out the analysis for 88 patients. The average age of the group of patients who declined to take part in the study was significantly higher than that of the population that was investigated (74 and 65 years, respectively). This selection may have resulted in an underestimation of the prevalence of osteoporosis being found, since apparently only the younger patients took part in the study.

The BMD at the lumbar vertebrae, the hip and the distal radius was measured for all 88 patients by means of a DEXA scan (Hologic QDR Delphi-C 70141). The BMD measured was expressed as a T-score.[14,15] A T-score of -2.0 SD or less at one of the positions measured together with a fracture was regarded as the treatment threshold.[13]

Statistical analysis was carried out using SPSS 10.0.7 for Windows. The protocol was submitted to the Medical Ethics Review Committee of the UMCG, who decided that the protocol did not fall under the scope of the laws regarding research in human subjects.

RESULTS

The general data of the patients are set out in *table 1* and the results of the telephone questionnaire in *table 2*. At the time of suffering the index fracture in 2001 all of the patients had at least one risk factor for osteoporosis: a low-energy fracture occurred after their 50th year (*table 2*). There was a positive family history (mother with a hip fracture) in 12 cases (14%), 6 patients (7%) had an osteoporotic vertebral fracture, 16 (18%) had a low body weight (<67 kg) and in 13 cases (15%) serious immobility played a part. Only one patient (1%) had long-term usage of more than 7.5 mg of prednisolone a day.

Of the 88 patients investigated, 45 had suffered a fracture prior to the index fracture in 2001 (*table 3*). Six patients were on calcium supplements (n=4) or bisphosphonates (n=2) before. Answers from the questionnaire indicated that osteoporosis had been confirmed in 12 patients (9.2%) in the group of 103 non-participating patients.

A DEXA was performed in 12 patients (14%) as response to the index fracture and in seven cases a low BMD was found. These and three other patients were referred to the department of internal medicine for further investigation and treatment. Six patients were prescribed calcium supplements, three patients vitamin D and one patient bisphosphonate. The initiative for further treatment had been taken equally by the surgeon, internist/rheumatologist and general practitioner (4, 3 and 3 times respectively).

Ten of the 88 patients (11%) who had not received further treatment were seen later on in the emergency department with a new low-energy fracture (wrist n=4, femur n=2, ankle n=2, humerus n=2). BMD analysis showed that in eight of these the T-score was less then -2.0 SD.

Table 1. *Patients characteristics (n = 88); averages with standard deviation (SD)*

Male : female	19 : 69
Age at date of index fracture (years)	65 (range 50-82)
Age at date of DEXA scan (years)	68 (range 53-85)
Height (m)	1.68 (SD 9.6; range 1.48-1.96)
Weight (kg)	77 (SD 12; range 50-110)
Body mass index	27.2 (SD 3.7; range 19.1-39.7)
Fracture site (number)	
• Proximal humerus	22
• Distal radius	50
• Hip	16
Conservative : operative treatment	53 : 35

Table 2. *Results of telephone questionnaire (n=88), numbers are presented*

Risk factors	
• Fracture after 50th year	88
• Positive family history	12
• Existing vertebral fracture	6
• Low body weight (<67 kg)	16
• Serious impaired mobility	13
• Use of corticosteroids	1
Number of risk factors per patient	
• 1	47
• 2	36
• 3	4
• 4	1
Medication at time of index fracture	
• Calcium	4
• Vitamin D	0
• Bisphosphonates	2
Medication started as result of index fracture	
• Calcium	6
• Vitamin D	3
• Bisphosphonates	1
Additional treatment	
• DEXA scan after fracture	12
• Consultation with internist	9
Specialist who initiated further investigations	
• Surgeon	4
• Internist /rheumatologist	3
• General practitioner	3
Previous fractures (number of patients)	45
Subsequent fractures (number of patients)	10

Table 3. *Fractures suffered before the index fracture in 2001 (57 fractures in 45 patients)*

Lower arm (proximal from wrist)	8
Wrist	22
Hand	5
Hip	3
Lower extremity (distal from hip)	13
Other sites	6

Note: 9 patients had had more than one fracture before 2001; 10 patients had another fracture after 2001, 7 of these had also had a fracture before 2001 (1 refracture of the wrist, 1 refracture of the ankle, the others were at new sites).

Table 4. *Bone mineral density (BMD) in the group investigated (n = 88)*

T< -2.5 SD (osteoporosis)	48	55%
-2.5 SD > T < -1.0 SD (osteopenia)	30	34%
Normal bone density	10	11%
T < -2 SD (treatment cut-off)	61	69%

After the three years of follow-up severe osteoporosis was found in 55% of the patients (WHO definition). With a BMD T-score treatment cut off of -2.0 SD, this was 69%. A normal bone density was found in 19% (*table 4*).

DISCUSSION

A fracture as a result of a low-energy injury in an older patient has long been identified as a risk factor for osteoporosis. In spite of this, our investigation shows that in three years only 14% of the patients were evaluated for osteoporosis in response to the index fracture. This is in accordance with the literature.[7-9]

The multidisciplinary approach in an FO clinic with the trauma surgeon as the starting point and an FO nurse practitioner as process manager, results in 75% of the patients at risk being investigated for the presence of osteoporosis and if necessary undergoing treatment.[13] The expectation is that this percentage will increase further by optimisation of the logistical process.

Our analysis of non-FO-patients three years after fracture shows that 55% have severe osteoporosis (fracture *and* T-score of -2.5 SD or less) while a total of 69% need to be treated with bisphosphonates. This percentage is comparable with the BMD data from our and other FO clinics.[8,13] In our opinion our results emphasise that an active approach towards case-finding of osteoporosis is urgently needed.

Questions can be raised as to whether this study with a relatively high percentage of non-participants can be compared with the results from the FO clinic. But the fact that the percentage of patients with manifest osteoporosis in both patient populations was equal may justify this assumption.

Of the 191 patients who were contacted, 103 could not participate. As they returned the answer card not all data from these patients were lost to the study. The average age of the non-participating patients was nine years older. This may imply that older patients, once they are out of clinical follow-up, are not interested or are not able to take part because of their age and comorbidity. Nevertheless, this large group of patients also deserves a tailored treatment immediately after they have suffered a fracture. The

percentage of osteoporosis in this group of patients can be expected to be even higher.

In the population investigated ten of the 88 patients (11.4%) suffered a subsequent fracture within three years, eight of them with osteoporosis. With bisphosphonates a relative fracture risk reduction of more than 50% can be achieved within one year. This means that one could speculate that a subsequent fracture could have been prevented in five of these ten patients.[10-12] This percentage of refracture agrees with the percentage found by Van Helden *et al.* in a recently published study.[16] They investigated a large number of patients (n=806) aged ≥50 years who suffered a fracture in 2000 as a result of a low-energy injury. One or more new fractures were found within a follow-up period of two to four years in 11.1% of the patients.

Although some kind of therapy was started at the time as a result of the former BMD measurements for ten of the 88 patients, only one was prescribed bisphosphonate. Even if the proper investigations had been initiated, they were generally not followed by effective treatment according to the guidelines.

The aim of this study was to obtain an impression of the extent of case-finding for osteoporosis. Our conclusion is that many fracture patients with underlying osteoporosis were unnoticed. Early treatment of osteoporosis results in a relative fracture risk reduction of more than 50% after just one year. According to good clinical practice, there is an urgent need for patients with low-energy fractures to be followed by case-finding for osteoporosis and subsequent treatment. Comparison with the first results from the FO clinic of the UMCG clearly shows that in patients aged ≥50 years, suffering a fracture is one of the most important moments for the start of an effective detection of osteoporosis. It is in the spirit of the existing modern guidelines. This initiative can best be taken at the location where the patient attends for treatment of the fracture, namely the emergency department in the hospital.

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CASE REPORT

Treating proteinuria in a diabetic patient despite hyperkalaemia due to hyporeninaemic hypoaldosteronism

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ABSTRACT

Diabetes mellitus is a common cause of hyporeninaemic hypoaldosteronism that might result in significant hyperkalaemia. We describe a patient with diabetic nephropathy and proteinuria who developed a remarkable hyperkalaemia on treatment with an angiotensin-receptor blocker. The management of hyperkalaemia and the pathophysiological background of hyporeninaemic hypoaldosteronism are discussed.

KEYWORDS

Diabetic nephropathy, hyperkalaemia, hyporeninaemic hypoaldosteronism, ACE inhibitor, angiotensin-receptor blocker

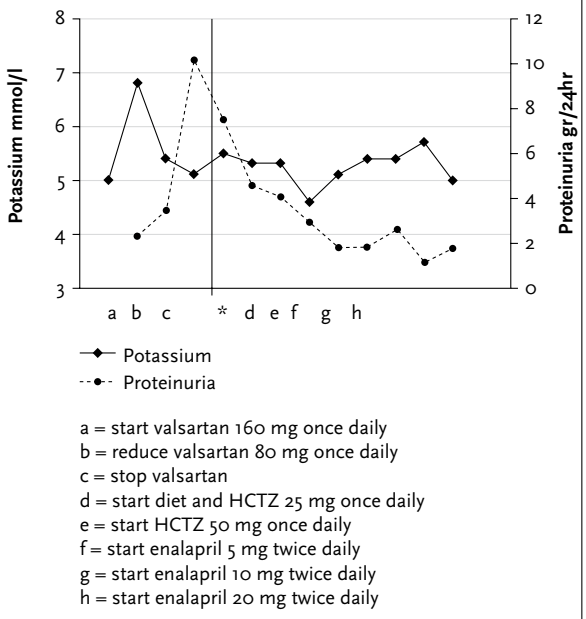
INTRODUCTION

Hyperkalaemia is a common problem in patients with diabetic nephropathy. It usually reflects the seriousness of renal dysfunction and limits the preferable treatment of diabetic nephropathy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers.[1,2] As diabetes mellitus itself is a risk factor for hyperkalaemia, even diabetic patients with normal renal function are vulnerable to develop hyperkalaemia as a result of such medication. Hyperkalaemia in these cases is generally mild. However, in patients with concomitant hyporeninaemic hypoaldosteronism this can be serious. We describe a patient with diabetic nephropathy and a normal glomerular filtration rate (GFR), who developed a potentially life-threatening hyperkalaemia during treatment with an angiotensin-receptor blocker.

CASE REPORT

A 55-year-old man had had documented type 2 diabetes mellitus, diabetic retinopathy, and polyneuropathy for three years. During treatment his metabolic control (HbA_{1C} 5.7%, stable body mass index 28.7) and blood pressure (130/70 mmHg) remained good, but he nevertheless developed proteinuria (0.54 to 2.19 g/day). His GFR, electrolytes and urinalysis were normal. Treatment for suspected diabetic nephropathy was started with the angiotensin II receptor antagonist valsartan 160 mg once daily. Other medications for diabetes and benign prostate hypertrophy included metformin 850 mg twice daily, glibenclamide 5 mg twice daily and alfuzosine 10 mg once daily. Hereafter, routine measurement of electrolytes revealed an asymptomatic hyperkalaemia with a potassium concentration of 6.8 mmol/l (*figure 1*). The valsartan was stopped, leading to a decreasing potassium level but escalation of the proteinuria without signs of the nephrotic syndrome. The potassium concentration remained slightly elevated and four weeks after discontinuation of valsartan, this was recognised to be due to hyporeninaemic hypoaldosteronism (*table 1*). The proteinuria was ascribed to diabetic nephropathy. To achieve normokalaemia, dietary measures were taken and hydrochlorothiazide (HCTZ) 25 mg once daily was started. The dosage of HCTZ was later increased to 50 mg once daily and finally the potassium concentration dropped to 4.6 mmol/l. Then, the ACE inhibitor enalapril was gradually started. Potassium levels remained within acceptable margins whereas proteinuria declined significantly but remained high (1.8-2.6 g/day). Further details on the course of potassium and proteinuria after each therapeutic step are shown in *figure 1*. As expected, there was no significant effect on blood pressure. During one-year further follow-up, the patient's proteinuria remained stable (1-2 g/day), while the GFR remained normal. Potassium levels ranged from 5.0 to 5.7 mmol/l.

Figure 1. *Course of potassium concentration in serum and proteinuria after each therapeutic intervention*



a = start valsartan 160 mg once daily
b = reduce valsartan 80 mg once daily
c = stop valsartan
d = start diet and HCTZ 25 mg once daily
e = start HCTZ 50 mg once daily
f = start enalapril 5 mg twice daily
g = start enalapril 10 mg twice daily
h = start enalapril 20 mg twice daily

*** corresponds with table 1. HCTZ = hydrochlorothiazide.**
Note: The periods between each measurement are approximately two weeks except the six-week period between c and d.

Table 1. *Basal data of plasma and urine values four weeks after discontinuation of valsartan.*

	Patient	Normal values
Blood		
Potassium	5.5	3.6-4.8 mmol/l
Sodium	144	136-144 mmol/l
Osmolality	292	260-300 mosmol/kg
Chloride	112	96-107 mmol/l
Bicarbonate	26	22-29 mmol/l
Glucose	7.8	3.5-5.5 mmol/l
Urea	8.3	2.5-7.5 mmol/l
Creatinine	110	70-133 µmol/l
HbA_{1C}	5.7	4.3-6.3 %
Plasma renin activity	0.30	<2.5 µg/l/u
Aldosterone	0.08	<0.35 nmol/l
Albumin	39	40-50 g/l
Total cholesterol	4.58	3.9-7.3 mmol/l
PH	7.38	7.35-7.45
PCO_2	5.9	4.5-6.0 kPa
Urine		
Potassium	132	25-100 mmol/24h (varies with intake)
Sodium	381	100-260 mmol/24h (varies with intake)
Volume	2350	ml, varies with intake
Creatinine	20.64	8.9-17.7 mmol/24h
Protein	7.43	<0.03 g/24h
Bence Jones protein	none	none
Osmolality	487	500-1400 mosmol/kg
Cortisol	203	55-220 nmol/24h
Aldosterone	<0.05	17-70 nmol/24h (normal diet)[a]
Calculated		
Creatinine clearance (GFR)	130	120-170 ml/min
TTKG	6.12	Varies with intake

TTKG = transtubular K^+ gradient = U_{K+} ÷ Uosm / Posm ÷ P_{K+}.
U_{K+}= urine potassium concentration (mmol/l); Uosm = urine osmolality (mosmol/kg); P_{K+} = plasma potassium concentration (mmol/l); Posm = plasma osmolality (mosmol/kg). Creatinine clearance = urine creatinine (µmol/24h) ÷ plasma creatinine (µmol/l) x 0.7
[a]Aldosterone secretion in urine was measured by a solid-phase radioimmunoassay (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, USA.

DISCUSSION

In diabetic patients the incidence of hyperkalaemia is higher than in the general population.[1,3] Exact numbers on its epidemiology are unknown, but one study examined the prevalence of hyperkalaemia in a diabetic population which appeared to be 15% (serum potassium >5.0 mmol/l).[4] Most cases could be explained by impaired GFR or precipitating drugs but proteinuria and retinopathy were also independently associated with higher median potassium levels. In this study, 2.3% of the diabetics had a serum potassium level >5.4 mmol/l while there was no evident cause.[4] In general, 50 to 75% of all cases with initially unexplained hyperkalaemia are due to hyporeninaemic hypoaldosteronism.[3,5] Based on these few studies we estimate that approximately 1% of the diabetic population with normal GFR might suffer from hyperkalaemia (>5.4 mmol/l) due to hyporeninaemic hypoaldosteronism.

The syndrome of hyporeninaemic hypoaldosteronism is characterised by the presence of inappropriately low aldosterone secretion either due to a reduced renin secretion in the kidney, a dysfunctional adrenal zona glomerulosa or a combination of both.[2] Patients typically present with borderline hyperkalaemia or asymptomatic hyperkalaemia precipitated by drugs such as ACE inhibitors, potassium-sparing diuretics and NSAIDs.

The pathophysiology of hyporeninaemic hypoaldosteronism is complex and seems to be multifactorial. In 85% of all patients with hyporeninaemic hypoaldosteronism, renin levels are below the normal margin suggesting a primary defect of renin secretion that causes secondary hypoaldosteronism. Renin is produced by the juxtaglomerular cells of the kidney and its production is influenced by many factors such as prostaglandins.[6] Inhibition of prostaglandins by NSAIDs reduces renin secretion which can induce reversible hyporeninaemic hypoaldosteronism. Other explanations for hyporeninaemia include damage to the juxtaglomerular apparatus, impaired conversion of precursors of renin to the active hormone, insufficient sympathetic stimulation of renin-producing cells by neuropathy, inhibition of renin release by hyperkalaemia, and physiological suppression of renin release by volume overload.[7-11]

In some patients with a normal plasma renin activity, aldosterone secretion can still not be stimulated by infusion of angiotensin, suggesting an intra-adrenal defect of aldosterone secretion.[3] In an attempt to stimulate aldosterone production, the plasma renin level may then rise to normal levels.

The diagnosis of hyporeninaemic hypoaldosteronism should be considered in every patient with an unexplained hyperkalaemia. A first step to establish the diagnosis is to measure the transtubular K^+ (potassium) gradient (TTKG) which gives an estimate on the ability of the kidneys to exchange potassium and sodium by the aldosterone-dependent Na^+-K^+-ATPase pump (for details and formulas see *table 1*). A TTKG below 7 in a hyperkalaemic patient strongly suggests hypoaldosteronism.[2] Further differentiation within the group of hypoaldosteronism (also known as type 4 renal tubular acidosis) can be made by measuring plasma renin activity and plasma aldosterone. Hyporeninaemic hypoaldosteronism is characterised by the combination of a decreased (or sometimes normal) renin level and a decreased aldosterone level while other causes of hypoaldosteronism are characterised by elevated renin levels.

ACE inhibitors or angiotensin-receptor blockers are strongly indicated to reduce proteinuria and progression of diabetic nephropathy.[12] However, in case of hyporeninaemic hypoaldosteronism this treatment is rather limited as it can lead to potentially life-threatening hyperkalaemia as seen in our case. Nevertheless there are some treatment options. Fludrocortisone is in theory the mainstay of therapy, since it corrects mineralocorticoid deficiency, but it should not be used because of its hypertensive effect. The approaches left are focused on decreasing gastrointestinal uptake by a low potassium diet and cation-exchange resin or increasing urinary potassium loss by either loop or thiazide diuretics.

We decided to treat our patient with a low potassium diet combined with increasing dosages of HCTZ until the potassium level became normal. Then an ACE inhibitor was started step by step with frequent control of potassium levels and accepting potassium levels up to approximately 5.5 mmol/l. Finally, full dosage of ACE inhibition could be administered. However, the proteinuria remained significant. Balancing the potential hazard of escalating hyperkalaemia against further reduction of proteinuria, with the addition of an angiotensin-receptor blocker, we decided to accept the proteinuria. The addition of sodium polystyrene sulphonate was not considered to be an option for chronic treatment because of its gastrointestinal side effects.

In conclusion, this report describes a typical case of hyperkalaemia due to (subclinical) hyporeninaemic hypoaldosteronism. The significance of this syndrome in the general diabetic population remains unclear but it is believed to be underdiagnosed by physicians, including internists.[13] We would therefore like to emphasise that it might be a common problem in patients with diabetic nephropathy. Preventive measures should therefore be routinely taken while treating such patients, including measurement of the TTKG in patients with initial borderline hyperkalaemia to detect subclinical hyporeninaemic hypoaldosteronism.

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CASE REPORT

Dengue shock syndrome and rhabdomyolysis

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INTRODUCTION

Dengue shock syndrome (DSS) is a life-threatening manifestation of one of the most common arboviral infections in humans. With the increased air travel to dengue endemic areas, healthcare providers in non-endemic countries are now frequently confronted with the initial symptoms of dengue in short-term travellers.[1] Although the course of dengue among this group of travellers is mostly subclinical, severe manifestations are also increasingly being reported.[2] This is the first case report concerning a short-term traveller describing the unusual presentation of dengue shock syndrome and serious rhabdomyolysis.

CASE HISTORY

A 66-year-old male with a history of hypertension and non-insulin-dependant diabetes mellitus (NIDDM) was admitted with complaints of fatigue, shivering, muscle, bone and joint pain, nausea, abdominal pain, diarrhoea, and tea-coloured urine. Five days before admission he returned from a two-week visit to Suriname, which he visited several times a year. He stayed in Paramaribo as well as in rural areas before the recent flooding. The abdominal symptoms started in Suriname two days before his return. The other symptoms presented on the day of his arrival. At that time he had not developed fever. He had not used any malaria prophylaxis, was not vaccinated against yellow fever and had not been bitten by a snake. One of his co-travellers developed abdominal symptoms that resolved spontaneously.

On admission the patient was moderately ill with a blood pressure of 119/87 mmHg, pulse 96 beats/min, breathing frequency of 14/min, oxygen saturation of 97% and a temperature of 37.2 °C. Physical examination was normal except for enlarged palpable submandibular lymph nodes.

Initial laboratory results (*table 1*) showed a thrombocytopenia and high levels of creatinine kinase, and elevated asparate aminotransferase and lactate hydrogenase. Also acute renal failure, mild hyponatriaemia, hypokaliaemia and hyperglycaemia were noted. Urine showed proteinuria and myoglobinuria. The ECG was normal. No fragmentocytes were seen in a blood smear.

Differential diagnosis included dengue, malaria, typhoid fever, leptospirosis, HIV, enteroviral infection and influenza. Also autoimmune disorders as polymyositis, dermatomyositis and vasculitis were considered.

Malaria was excluded by repeated negative blood smears. Serological tests for leptospirosis, HIV, hepatitis B and C virus, influenza A and B virus, para-influenza virus, RS virus, adenovirus, *Chlamydia psittaci*, *Chlamydia pneumoniae* and *Coxiella burnetii* were all negative. There was no serological evidence of active hepatitis A, Epstein Barr virus, or cytomegalovirus infection. Cell cultures were negative for respiratory viruses. Stool examination revealed no pathogens. Bone marrow aspiration showed no evidence of tuberculosis or leishmaniasis. Finally serological tests for autoimmune diseases were also negative (*table 1*).

During the first day of admission, the patient developed high fever up to 39.3 °C with an increasing CK level up to a maximum of 156,900 U/l on day 2. On day 3, the patient complained of severe abdominal pain accompanied by dyspnoea and tachycardia. Inflammatory response parameters were now substantially elevated. Additional computed tomography imaging showed no pathology except for inhomogenic consolidation of the lower lung lobes. Despite empiric treatment with broad-spectrum antibiotics for a suspected pneumonia, the patient deteriorated and was transferred to the intensive care unit the following day and intubated because of respiratory failure. The condition of the patient further deteriorated. A septic shock developed, complicated by multiple organ failure. Anuric renal failure and progressive generalised oedema developed accompanied by oropharyngeal and nasal bleeding. Fever persisted from day one to three and day five to seven. Nine

Table 1. *Laboratory values*

	Day 1	Day 2	Day 4	Day 5	Reference values
CRP (mg/l)	12	33	492	510	<5
ESR (mm/h)	23	31			<7
Hemoglobin (mmol/l)	10.3		8.0	5.8	8.6-10.7
Hematocrit (l/l)	0.47	0.41	0.38	0.27	0.39-0.49
Platelets (G/l)	18	26	147	93	150-300
Leukocytes (G/l)	6.8	6.7	6.3	11.8	3-10
Sodium (mmol/l)	127	128	134	139	137-143
Potassium (mmol/l)	3.0	3.9	3.1	3.4	3.5-5.0
Creatinine (µmol/l)	138	138	160	315	50-120
Urea nitrogen (mmol/l)	12.2	10.1	10.5	19.8	3.0-8.3
CK (U/l)	141,010	156,900	61,700	18,413	<175
ASAT (U/l)	1520	1583	1337	1494	<30
ALAT (U/l)	202	201	250	421	<40
LDH (U/l)	12,496	11,703	7299	5431	225-450
Bilirubin (µmol/l)	24	24	46	44	<17
APTT (sec)			60		31-39
PTT (sec)			19		11.7-15.7
Fibrinogen (g/l)			7.8		1.7-3.3
D-dimer (µg/l)			1719		<500

Autoimmune serology negative (ANA, ANCA, anti-dsDNA, ENA RNP, SS-A/SS-B antibodies, Sm/Jo-1 antibodies, ACLA). CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; CK= creatine phosphokinase; ASAT = aspartate aminotransferase activity; ALAT = alanine aminotransferase activity; LDH = lactic dehydrogenase activity; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; anti-dsDNA = anti-double-stranded DNA antibodies; ENA RNP = extractable nuclear antigen ribonucleoprotein ACLA = anticardiolipin antibodies.

days after admission dengue virus infection was diagnosed by high levels of IgM and IgG antibodies against dengue virus antigen.

Despite aggressive shock treatment and adequate treatment of secondary infections (pneumonia, central catheter infections, oral candidiasis), bleeding complications and renal failure, the patient developed a progressive respiratory failure due to fibroproliferative ARDS with hypercapnia and low compliance resulting in death on day 47.

DISCUSSION

Dengue virus is an arbovirus and a member of the *Flaviviridiae* family. The virus is transmitted from humans to humans by the bite of infective female *Aedes aegyptii* mosquitoes during daytime in endemic (sub)tropical regions. To a lesser degree *Aedes albopictus* and *Aedes polynesienses* are involved in the transmission of this virus. So far four distinct serotypes of dengue viruses have been reported (DENV-1, DENV-2, DENV-3 and DENV-4). As a result of uncontrolled urbanisation in tropical countries and increased global air travel, dengue has now become the most important arthropod-borne viral disease in humans.[3] Today approximately 50 to 100 million cases of dengue fever (DF) and 500,000 cases of dengue haemorrhagic fever (DHF) occur annually, resulting in about 24,000 deaths worldwide (average mortality rate of 5%).

So far a fatal course of dengue has primarily been reported from tropical regions. DHF and dengue shock syndrome (DSS) are the leading causes of morbidity and mortality among children in South East Asia.[4] DSS is reported to be the third leading cause of ARDS in paediatric intensive care in Dengue endemic areas after sepsis and pneumonia.[5,6]

The incidence of dengue infection in short-term travellers returning from dengue endemic areas is underestimated due to its subclinical course. In a prospective study among 447 Dutch short-term travellers to Asia an incidence of 2.9% was found.[1] Since repeated infection with another serotype has been associated with increased risk of severe manifestation, the number of short-term travellers developing a potentially life-threatening DHF/DSS is expected to increase.

The clinical spectrum of dengue ranges from an asymptomatic course to serious manifestations of a potentially fatal dengue shock syndrome (*table 2*). Prognosis is usually good and the disease is self-limiting in most cases. But the fatality rate once shock has set in may be as high as 44%.[7,8]

No specific treatment of dengue exists.[8] High-dose methylprednisolone failed to reduce mortality in severe DSS; however prolonged thrombocytopenia in DHF has responded well to corticosteroids.[4] So far effective drugs that block the increased vascular permeability are not available.[9] Positive results from high-dose immunoglobulin and activated factor VII on haemostasis have been reported.[10-12]

Table 2. *Clinical spectrum of dengue ranges from an asymptomatic course to a potentially fatal dengue shock syndrome*

Dengue fever (DF)
- Fever lasting 5-7 days, sometimes biphasic or 'saddle-back' fever curve
- Symptoms of frontal headache, retro-ocular pain, myalgia, arthralgia, nausea, vomiting, diarrhoea and maculopapular or diffusely erythematous rash
- Leucopenia and mild thrombocytopenia are frequent findings
- Minor haemorrhagic manifestations such as petechiae, epistaxis and gingival bleeding usually 3-4 days after onset of fever
- Prognosis favourable and recovery usually after 7-10 days

Dengue haemorrhagic fever (DHF)
- Acute febrile illness similar to DF with haemorrhagic manifestation
- Thrombocytopenia <100 x 10 x 6/l
- Evidence of plasma leakage caused by increased vascular permeability leading to oedema, serous effusion, haemoconcentration, hypoalbuminaemia

Dengue shock syndrome (DSS)
- DHF with circulatory failure characterised by a rapid, weak pulse with narrowing of the pulse pressure (<20 mmHg, regardless of blood pressure levels), or hypotension with cold clammy skin and restlessness

The extent of thrombocytopenia does not predict clinically significant bleeding so platelets should not be administered just upon platelet count. In contrast, prolonged duration of shock and haematocrit within the normal low range at the time of shock have been associated with increased risk of severe haemorrhage.[13]

Patients with secondary infections with dengue virus are at more risk of developing DHF/DSS. The already existing non-neutralising cross-reactive antibodies seem to enhance virus uptake and replication in mononuclear cells leading to high viral load with subsequent enhanced release of cytokines, which may explain the increased risk of developing DHF/DSS. Other risk factors include infection with a more virulent genotype, young age, Caucasian race and a history of asthma, diabetes and sickle cell anaemia.[4] Lower incidence in blacks suggests genetic susceptibility. Surprisingly malnourished patients are relatively protected probably due to suppressed immune response.[12-14]

Although we could not distinguish by antibody response between a primary or secondary infection in our patient, a secondary infection seems more likely. The patient travelled frequently to endemic areas and furthermore IgG antibodies against other arboviruses with the same vector (Yellow Fever and Japanese encephalitis) were present.

Several unusual manifestations of dengue virus infections have been reported, such as hepatic failure, cardiomyopathy, encephalopathy and encephalitis. However, severe rhabdomyolysis and its complications are not mentioned as a potential manifestation of dengue in review articles and textbooks. It is believed to be an underrecognised and underreported entity which has been reported in only five patients.[15,16] Our patient presented with severe rhabdomyolysis with a peak CK level of 156,900 U/l complicated by renal failure. It should be emphasised that the risk of renal failure could be decreased by early detection of rhabdomyolysis by routine measurement of CK level in patients with suspected dengue infection and subsequent adequate treatment.

Although in our patient dengue was included in the differential diagnosis at first presentation, alarming signs of impending shock were not recognised. The severe abdominal pain was explained as a symptom of developing pneumonia, which was noted in lower lobes on CT-abdomen. Established shock and elevated CK level subsequently resulted in a cascade of renal failure, haemostatic derangement with bleeding complications, secondary infections, and respiratory failure due to progressive ARDS with eventually a fatal course. Perhaps the clinical outcome would have been different if alarming signs had been recognised on time and shock could have been prevented.

CONCLUSION

The number of short-term travellers presenting with primary and secondary dengue infections after returning from dengue endemic regions is expected to increase. So far no specific treatment or effective vaccine is available, and vector eradication programmes have not been successful. In addition, the extent of this disease could even increase by potential extension of the habitat of dengue transmitting vectors due to climate change. Therefore healthcare providers in non-endemic regions should be aware of the alarming symptoms of severe dengue infections since early recognition and prevention of shock by fluid resuscitation is the only effective treatment in patients with DSS. Finally, CK levels should be routinely measured in patients with suspected dengue in order to prevent acute myoglobinuric renal failure due to severe rhabdomyolysis.

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PHOTO QUIZ

Peritonitis

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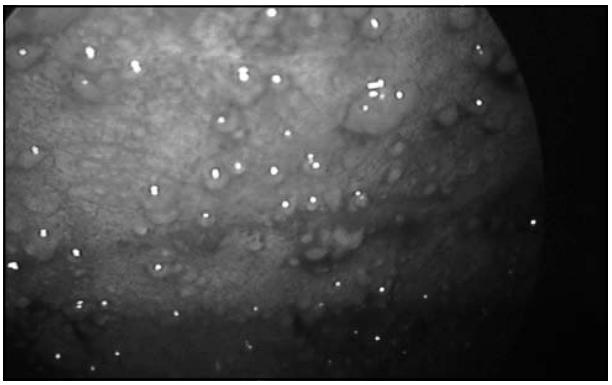
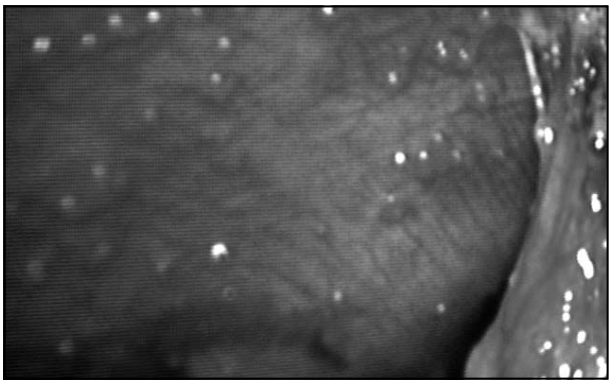
CASE REPORT

A 35-year-old North African man without a previous medical history was admitted with abdominal discomfort. On examination the patient was not acutely ill. His temperature was normal. Lymphadenopathy was absent. Tense ascites was evident but there were no stigmata of chronic liver disease.
Extensive laboratory testing only revealed a C-reactive protein of 93 mg/l and an erythrocyte sedimentation rate of 51 mm. Haematological and biochemical tests were unremarkable. Especially the liver function and cholestatic parameters were within the normal limits. HAV-IgM, HbsAg, anti-HBc and anti-HCV were all negative.
Chest X-ray was normal. Abdominal ultrasound confirmed the ascites, but revealed no other abnormality.
As differential diagnosis we thought of hepatic vein obstruction, nonhepatic causes of ascites and intra-abdominal disorders. There was no reason to consider alcoholic or viral liver disease. In order to obtain ascitic fluid we performed a percutaneous aspiration. On analysis, yellow clear ascites revealed a leucocyte count of 2.1 x 10*9/l with 70% lymphocytes. Albumin 30 g/l, serum albumin-ascites gradient (SAAG) was 3 g/l. Cytology was negative and microscopy revealed no acid-fast bacilli (Ziehl-Neelsen stain). A polymerase chain reaction (PCR) on *Mycobacterium tuberculosis* complex in the ascitic material was negative.
In the meantime a computed tomographic (CT) abdominal scan with intravenous contrast was carried out with remarkable contrast staining of the peritoneum. The abdominal organs, vessels and intra- and extrahepatic bile ducts were normal.
A diagnostic laparoscopy was performed, which revealed typical peritoneal nodules (*figures*).

WHAT IS YOUR DIAGNOSIS?

See page 85 for the answer to this photo quiz.

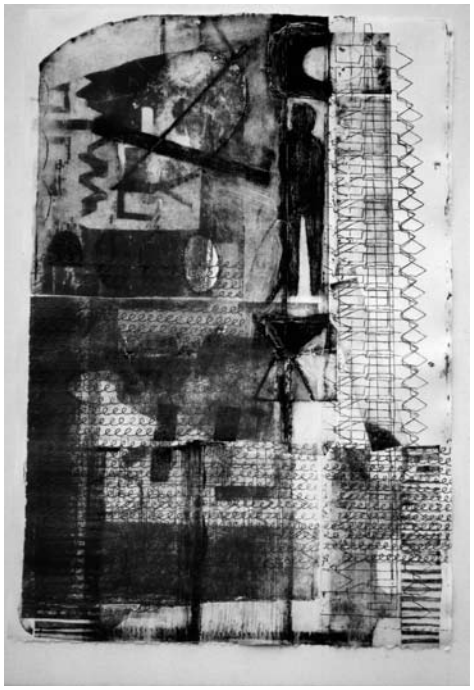




ABOUT THE COVER

Untitled

Frans de Groot and Josée Wuyts



This month the cover presents a print made by two artists, Frans de Groot (1949) and Josée Wuyts (1961). Since 1990, they have been working together to set up several graphic projects. One of these is the House project, which this month's cover is part of. De Groot and Wuyts work around a theme of the human figure in relation to abstract typographical subjects. Each print contains elements brought in by both artists. Both artists are members of the Dutch Vereniging voor Originele Grafiek (VOG, Association for the Original Print). Besides their joint exhibitions in the Netherlands but also abroad, in the England, Bulgaria, Russia and the USA, they also expose their own work separately.

An original print is available at a price of € 200 and can be ordered from Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by mail: galerie-unita@planet.nl or www.galerie-unita.com

MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles that were published in the November issue of the Netherlands Journal of Medicine. This is based on analysis of our user log file on 10 January 2006 (www.njmonline.nl).

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ANSWER TO PHOTO QUIZ (ON PAGE 82)

PERITONITIS

DIAGNOSIS

A diagnostic laparoscopy was carried out because the results so far warranted considering tuberculous peritonitis in our differential diagnosis. Culture growth of *Mycobacterium tuberculosis* of ascites or peritoneal biopsy is the gold standard test. Polymerase chain reaction (PCR) in the biopsy material of the typical nodules was positive and on microscopy a granulomatous inflammation with necrosis was seen, compatible with tuberculosis. Ziehl-Neelsen staining and auramine tests were negative. Later on the culture test confirmed *Mycobacterium tuberculosis* disease with a normal antibacterial resistance pattern.
Considering the laparoscopic findings and the laboratory results we immediately started a six-month course of first-line antituberculous drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. There was a full recovery during follow-up in the outpatient clinic. No side effects were observed. The local health service was helpful in watching over drug compliance.

REMARKS

The symptoms and signs of peritoneal tuberculosis are non-specific, and unless a high index of suspicion is maintained, the diagnosis can be missed or delayed resulting in increased morbidity and mortality.[1] Laparoscopy with directed biopsy is currently the best way to make a rapid specific diagnosis. A PCR on *Mycobacterium tuberculosis* complex can be carried out, with a result within one day. Other methods to demonstrate the acid-fast bacilli are Ziehl-Neelsen staining or the auramine test. In case of peritoneal tuberculosis the chance of a positive auramine or Ziehl-Neelsen test in ascitic material is only 10% and culture growth is falsely negative in 70% of the cases. It is therefore essential to take a peritoneal biopsy for culture.[2]
Laparoscopy and peritoneal biopsy is a safe procedure and has many advantages. In case of tuberculosis the typical peritoneal adhesions and the whitish caseating granulomatous inflammation i.e. nodules or tubercles are seen.[3] It enables targeted tissue biopsy specimens to be obtained from the peritoneum, thus allowing a rapid diagnosis, while other conditions, such as peritoneal lymphoma and carcinomatosis, are excluded. Laparotomy, which is associated with a mortality of 3 to 12% in patients with tuberculous peritonitis, may also be avoided.[4]

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3. Bhargava DK, Shriniwas, Chopra P, et al. Peritoneal tuberculosis: laparoscopic patterns and its diagnostic accuracy. Am J Gastroenterol 1992;87:109-12.
4. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol 1993;88:989-99.

INFORMATION FOR AUTHORS

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

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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.

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

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