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EDITORIAL

Autointoxication – from caregiver frustration toward research challenge

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ABSTRACT

Autointoxications are among the most common medical emergencies. Patterns of toxicosyndromes show regional variation, and they change over time. Intoxications are usually multiple. Although autointoxication is often self-limiting and a fatal outcome is unusual, suicide attempts may kill. Toxicity screening, emergency room first aid, decision rules for admission to the Ward or the ICU, or prolonged observation in the Emergency Department, and measures to prevent gastrointestinal substance resorption are based on expert opinion rather than scientific evidence. Toxicity screening needs regular adjustment and should be individually tailored, based on local patterns as well as on clinical syndromes. A team approach and efforts to study safe management strategies should turn caregiver frustration into a more enthusiastic and inquisitive attitude towards the challenges to meet the medical needs of these patients.

This issue of the Journal contains two contributions on different aspects of autointoxication. Drug-related problems including autointoxication and drug overdose or abuse are common; they comprise 4% of all cases presenting to emergency departments of teaching hospitals.[1] Autointoxication was by far the most frequent diagnosis made by residents in internal medicine during after-office hours in the Groningen University Hospital.[2] Although regularly confronted with autointoxication, many internists have a sense of frustration with every new patient brought in. This patient group usually survives anyway.[3-5] Health workers find it difficult to sympathise with their self-inflicted injuries. Moreover, their basic problem is a mental, not a physical condition. The expertise needed to manage the underlying condition lies in the field of psychiatry, and not internal, emergency or intensive care medicine. Despite psychiatric interventions, attempted suicide is often followed by repeated attempts that may eventually be fatal.[6] Indeed, in younger age groups, attempted suicide including auto-intoxication with an array of pharmaceutical products and abuse of 'recreational' drugs, is a leading cause of death.[7]
Today, we try to anchor our teaching and training in internal medicine on a basis of scientific evidence. For the sake of transparency and accountability towards patients, and to prevent mistakes and mishaps, as well as to improve the teaching process, many diagnostic and therapeutic decisions are now based on protocols and guidelines. Local protocols are in turn based on evidence-based guidelines published in the literature by expert committees from national and international scientific organisations.
Clinical toxicology is difficult to manage by guidelines because of the vast array of toxicosyndromes and an even longer list of different toxic agents. Its knowledge base is built on various and numerous case reports, and prospective randomised trials in patients are scarce. Even if certain intoxications were common, randomised studies would be difficult to conduct as consent cannot be obtained from patients with impaired consciousness. Yet certain general principles apply to the majority of cases of intoxication. One such example of the general management of victims of autointoxication by ingestion includes measures to prevent further resorption of toxic substances from the intestinal tract. Gastric lavage, activated charcoal and whole bowel lavage have such potential advantages, but there are also potential adverse effects, including the risk of aspiration of gastric lavage fluid and activated charcoal into the airways in patients with impaired consciousness.

To prevent aspiration, intubation of the airway would seem to be a good idea, but this strategy is possibly unnecessarily aggressive for mildly intoxicated patients, and risks incurred by anaesthesia should be considered. The available evidence suggests that potential benefit of gut decontamination cannot be expected if these measures are delayed until 30 to 60 minutes after ingestion.[8-10] Intoxication does not necessarily happen at one point in time but may take several hours and the time of ingestion is often unknown. In one study, 63 patients with serious autointoxication requiring admission to hospital could report the time of ingestion. Only 15 (24%) of these patients presented within one hour after their intoxication.[11] Activated charcoal was given to ten of these 15 patients, but only four received the compound within one hour after autointoxication. Gastric lavage,[12] whole bowel lavage[13] and activated charcoal[14,15] have all been addressed in international guidelines,[16] but these are based on low-level or controversial evidence.[17,18] Many of the guideline-derived recommendations are poorly adhered to,[19] possibly because they may be impractical.

Guidelines for decision-making in diagnostic screening, for admission to the ward or to the intensive care unit, with intubation and mechanical ventilation, or haemodialysis, or specific antidotes are even more controversial. Very few studies have addressed these case management problems,[20] and there is clearly a need for more scientific evidence to guide decisions. For some interventions, such as the infusion of sodium bicarbonate to victims of tricyclic antidepressant overdose,[21,22] the evidence may be low but the treatment is cheap and relatively harmless, while the potential benefit is great and therefore does not seem to justify expensive research.[23]

By necessity, guidelines result from consensus among experts who review and interpret the available scientific evidence. The process of finding consensus is slow and a guideline may not always be applicable in all areas in the world. There are huge differences in patterns of auto-intoxication between regions in the world.[24-26] Patterns of common toxicosyndromes may also change over time, with the newly recognised toxicity patterns of recreational drugs such as ecstasy (MDMA) and gamma-hydroxybutyrate (GBH).[27-29] The report by Vermes *et al.* (page 168 of this journal) from the Erasmus Medical Centre in Rotterdam is therefore useful as it reflects an inner city toxicosyndrome epidemiology and serves as an update that may help other centres to adapt and improve their screening procedures. International standards and guidelines may be helpful but toxicity screens that apply in one area in the world need not necessarily apply in other areas, and regular updates are necessary to correct for changing patterns in intoxication over time.[30,31] Drug screening should rather be targeted specifically to the clinical presentation (the 'toxicosyndrome')[32] combined with usual patterns derived from relevant regional occasional surveys such as the Rotterdam survey. The report by Meulendijks *et al.* (page 164 of this journal) from the University Medical Centre St Radboud in Nijmegen, is a useful initiative to help design a general guideline for the management of victims of autointoxication in the emergency department. In their study population, many patients could be discharged home safely after an observation period of four to six hours in the emergency department. Their intoxications were mild, predominantly with benzodiazepines which apart from sedation and hypoventilation have a relatively mild toxicity profile. The authors rightly mention that their decision-making guideline should be validated in a prospective multicentre study. The management of common problems calls for increased research efforts. Intoxications are common diagnoses, and their treatment deserves a cost-effective management strategy based on scientific evidence. Funding should come from national scientific research grants such as Zon-NW (the Netherlands Medical Sciences Care Trial).

Meanwhile, patients with autointoxication deserve our care and commitment. Their mental problems and social behaviour challenge our professional attitude. Also, our clinical skills are challenged in suspecting and detecting the causes of their syndrome. Many patients have ingested multiple toxic substances,[33] and laboratory results should be interpreted with great care. Treating these patients does not need to be frustrating – their treatment is far from futile. Their self-inflicted injury may cause them to die from complications but their short-term prognosis is excellent, provided that treatment is adequate.

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REVIEW

Blood products and parvovirus B19

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ABSTRACT

A Committee of the Health Council of the Netherlands has expressed its opinion on introducing testing of blood products for parvovirus B19 (B19). Although infections with B19 generally run their course without any serious health problems, for some groups, such as pregnant women, patients with underlying haematological problems and patients with immunodeficiency, infections with B19 can result in serious complications. For cellular blood products, which are derived either from a single donor or a limited number of donors and are administered either to a single patient or to a limited number of patients, the Committee recommends that a risk-group approach be adopted and that 'B19-virus safe' blood products be administered to the risk groups mentioned above. The Committee defines as 'B19-virus safe' cellular blood products from a donor in which IgG antibodies against B19 have been detected in two separate blood samples, one taken at least six months after the other. Patients other than those in the risk groups should continue to receive cellular blood products that have been produced in accordance with current safety criteria. For plasma products, which are prepared from plasma pools and are administered to large numbers of patients, the measures must be aimed at cutting down the levels of B19 infectivity in such pools. For plasma pools, the Committee proposes a maximum permissible limit of 10^4 genome copies of B19 per ml.

INTRODUCTION

Infections with parvovirus B19 (henceforth referred to as B19) are quite common, particularly in children.[1,2] The most widespread clinical picture caused by B19 is erythema infectiosum, which is also known as 'Fifth disease'. In otherwise healthy individuals, the infection generally runs its course without any problems. In some groups, however, such as pregnant women, patients with underlying haematological problems and patients with immunodeficiency, B19 infections can result in serious complications. Current attempts to maximise the safety of blood and blood products focus on entirely eliminating the risk of transmitting infectious agents. This has led to a wide range of screening tests. The general introduction of such tests for hepatitis B virus, hepatitis C virus and HIV has greatly reduced the risk for transmission.[3,4] It would also be possible, but expensive, to test all blood products for the presence of viruses such as B19 and cytomegalovirus, the transmission of which is a risk for only some of those using these products. A Committee of the Health Council of the Netherlands has expressed its opinion on the introduction of such tests for B19.[5]

In its deliberations, the Committee has drawn a distinction between cellular blood products, which are prescribed relatively frequently, and products derived from plasma such as coagulation factors, which are less frequently prescribed. Cellular blood products are derived either from a single donor or a limited number of donors. These products are administered to, at the most, a limited number of patients. Plasma products are prepared from plasma pools, which are sometimes derived from very large numbers of donors and are administered to large numbers of patients.

PARVOVIRUS B19 INFECTIONS

B19 is one of the nonenveloped viruses. With a particle size of 20 to 30 nm, it is one of the smallest DNA viruses.[6] For the purpose of replication, B19 is dependent on erythroid precursor cells in the bone marrow. These cells are destroyed by the process of viral replication. B19 is usually transmitted by coughing, but it can also be acquired by blood transfusions or, if a pregnant woman becomes infected, it can be passed from mother to unborn child. Infections with parvovirus B19 are quite common. It is estimated that in the Western world 50% of all 15-year-olds have experienced an infection.[6] Even higher percentages can be seen in the elderly, possibly as high as 80 or 100%.[1]

The diagnosis of a B19 infection is traditionally based on serological screening tests. Such tests make use of the antibodies that are produced in response to a viral infection. More modern tests, based on the detection of viral DNA, are now available. Some examples are the dot-blot test and the nucleic acid amplification test (NAT). The result of the latter test is given in number of complete copies of viral DNA (genome copies).

After B19 infection, most individuals form anti-B19 antibodies and recover with few problems. The anti-B19 antibodies persist throughout life.[7] In some groups, however, B19 infections can result in serious complications or health problems. Infection during the second trimester of pregnancy results in an approximately 10% increase in prenatal mortality and in 3% of cases leads to hydrops foetalis.[8,9] Recently published data indicate that there is also an elevated risk during the last part of pregnancy.[10]

In patients with underlying haematological problems, such as patients with congenital haemolytic anaemia, infection by B19 can result in an aplastic crisis.[2,6] B19 can persist in patients with cellular immunodeficiency, for example resulting from a HIV infection, or from treatment with immunosuppressive drugs following organ transplantation. This can cause long-lasting bone marrow damage and aplasia, not only of red blood cells,[2] but also of other cell types.[11]

Recent publications on research into small, selected groups of patients suggest that B19 infections can persist for a protracted period of time in patients with an apparently intact immune system.[12,13] Persistence of B19 was also demonstrated in bone marrow[12] and synovial membrane,[14] but not in blood, of healthy individuals.

Chronically infected individuals are treated with immunoglobulin preparations, which are administered intravenously.[2] The action of these preparations is probably based on the presence of anti-B19 antibodies.

PREVALENCE OF B19 IN BLOOD DONATIONS AND PLASMA POOLS

The reported prevalence of B19 in blood donations varies from 0.03% to 0.6%.[15-19] No data have been published concerning the prevalence of B19 in Dutch donors.

DNA of B19 can be detected in more than 60% of the plasma pools used for the production of plasma products, though usually in relatively small quantities.[20,21] The products derived from these pools also contain B19 DNA.[20] The higher viral titres found in some pools are probably caused by a small number of highly contaminated donations. The infectivity of plasma given to individual patients is dependent on the level of the viral titre.[22] This has led to the conclusion that the reduced infectivity of plasma with low titres of B19 DNA is caused by binding of anti-B19 antibodies to the viral particles.[20,23]

RECOMMENDATIONS

The Committee has drawn a distinction between cellular blood products and plasma products.

In the case of cellular blood products, the Committee recommends a risk-group approach in which 'B19-virus safe' blood products are administered to risk groups. In this way, patients for whom infection with B19 could cause problems will be given maximum safety blood products. This approach is in keeping with measures previously used in blood transfusion medicine with respect to cytomegalovirus transmission. The Committee defines as 'B19-virus safe' cellular blood products from a donor in which IgG antibodies against B19 have been detected in two separate blood samples, one taken at least six months after the other. The Committee has opted for this double test since the virus can persist for some time after IgG antibody formation has started. After six months, the antibodies will have resulted in removal of B19 from the blood.

The Committee recommends that B19-virus safe cellular blood products be administered to pregnant women (except in the case of transfusions given during birth), patients with congenital or acquired haemolytic anaemia who have no detectable antibodies to B19 and patients with cellular immunodeficiency who have no detectable antibodies to B19. The Committee takes the view that anti-B19 antibody testing is not feasible in the case of pregnant women, since an emergency blood transfusion may be required in some cases. In such an event, there is no time to carry out tests for the presence of antibodies.

The Committee points out that it has not yet been established whether others, such as patients with other haematological problems who require transfusions, are categorically at high risk. There is probably a wide range of individual variation. The Committee urges that further

research be carried out in this area. Patients other than those in the risk groups should continue to receive cellular blood products that have been produced in accordance with current safety criteria. The Committee emphasises that the prescription of blood products to individual patients remains the responsibility of their attending physician. The risk-group approach that is recommended for cellular products cannot be used for plasma products, given their large-scale production and use. The measures used for plasma products must be aimed at cutting down the levels of infectivity in such pools. Highly infected donations should be identified and removed before the individual samples are pooled. For final pools, the Committee proposes a maximum permissible limit of 10^4 genome copies of B19 per ml. Earlier, the American Food and Drug Administration (FDA) suggested a similar maximal load.[22]

CONCLUDING REMARKS

Technical developments, such as the inactivation of micro-organisms[24] and the use of nanofiltration[25] to cut down the number of viral particles in the final product, can lead to other options for making blood products B19-virus safe. The Committee feels that its proposal should be reviewed when it becomes feasible to incorporate these techniques into standard blood bank procedures. However, no such development is expected for several years.
A recently published study in a small, selected group of patients with apparently intact immune systems indicates that B19 can persist in bone marrow.[12] The Committee considers this initial report to be quite remarkable, and it urges that further research be carried out. The Committee would like to draw attention to the possibility of B19 infection in recipients of bone marrow transplants.
Finally, the Committee would like to emphasise that in the Netherlands, although being treated with blood products always involves an element of risk, even the 'standard' blood products are extremely safe.

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Aplastic anaemia: a review

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ABSTRACT

Aplastic anaemia is featured by bone marrow hypocellularity and peripheral pancytopenia and is a potentially fatal disease. In recent years, insight in its pathogenesis has increased. It appears that activated autoreactive T lymphocytes induce apoptosis of haematopoietic stem cells resulting in a hypocellular bone marrow. Nowadays, it can be treated by stem cell transplantation or immunosuppressive therapy. This review focuses on the pathophysiology and treatment of aplastic anaemia.

INTRODUCTION

Aplastic anaemia is a serious medical disorder which, when untreated, has a median survival of less than ten months[1] due to infections and haemorrhage. Fortunately, in the last decades its prognosis has improved dramatically and most patients now achieve durable responses. Aplastic anaemia is featured by hypoplasia of the bone marrow and peripheral pancytopenia (*figure 1*). The most commonly used criteria for the diagnosis aplastic anaemia are marrow cellularity of less than 25% of normal or less than 50% with haematopoietic cells representing less than 30% of the residual cells and at least two of the following peripheral blood counts: neutrophil count of less than 0.5 x 10^9/l, platelet count of less than 20 x 10^9/l, and/or anaemia with a reticulocyte count of less than 1%.[2]
Aplastic anaemia can be due to congenital (20%) or acquired causes (80%) (*table 1*). Congenital diseases leading to aplastic anaemia will not be further discussed here.

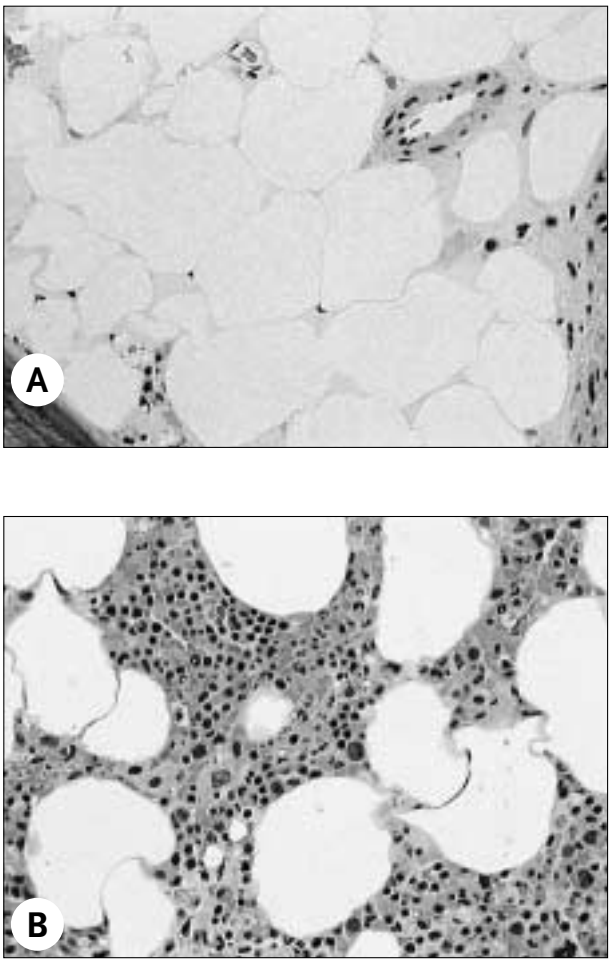

Figure 1
Bone marrow biopsy from a patient with aplastic anaemia (A) compared with a normal bone marrow (B)

Causes of acquired aplastic anaemia are very diverse, the most common being iatrogenic causes such as radiation and drugs directly cytotoxic to the bone marrow. Some haematological malignancies or infections can present as aplastic anaemia. In some cases, myelodysplastic syndrome (MDS) can occur with a hypocellular bone marrow and peripheral pancytopenia. In these cases, it is sometimes difficult to distinguish between MDS and aplastic anaemia. Distinction by cytogenetic analysis is not always possible because in about 4% of the patients with aplastic anaemia cytogenetic abnormalities are found, sometimes similar to those seen in patients suffering from MDS.[3] Furthermore, not all patients with evident morphological MDS have cytogenetic alterations. Some institutions consider patients with findings fulfilling the diagnosis of aplastic anaemia and with cytogenetic abnormalities as MDS, independent of the marrow morphology.[4]
The management of acquired aplastic anaemia due to such causes as aforementioned involves treatment of the underlying cause. This review, however, will focus on the remaining causes of acquired aplastic anaemia in which haematopoietic stem cell damage due to autoreactive T lymphocytes is the central event but in which the exact cause that elicits this reaction is largely unknown.

Table 1
A classification of aplastic anaemia

CONGENITAL	
Fanconi anaemia	
Shwachman-Diamond syndrome	
Dyskeratosis congenita	
Amegakaryocytic thrombocytopenia	
ACQUIRED	
Idiopathic	
Haematological malignancies	Hypocellular MDS
	Hairy cell leukaemia
	Acute lymphatic leukaemia
Infectious	Posthepatitis
	Parvovirus B19
	HIV
	Mycobacterial infections
	EBV
Toxic	Radiation
	Cytostatics
	Idiosyncratic
	Pregnancy
Autoimmune disorders	Eosinophilic fasciitis
	GVHD

EPIDEMIOLOGY AND AETIOLOGY

Aplastic anaemia is a rare disease with a reported incidence of approximately 2 per 1 x 10^6 annually in Europe. In Asia, it occurs three times more often with an incidence of 5 to 7 per 1 x 10^6 annually.[5]
As will be described below, autoreactive T lymphocytes are thought to play an important role in the pathogenesis of aplastic anaemia. As in other autoimmune diseases, an association with certain HLA alleles has been described in patients with aplastic anaemia. In these patients, an increased HLA-DR2 frequency of 58% is found, versus 28% in the normal population.[6]
Because prognosis of aplastic anaemia is related to the number of neutrophils, aplastic anaemia is divided into nonsevere aplastic anaemia with neutrophils above 0.5 x 10^9/l, severe aplastic anaemia with neutrophils between 0.2 and 0.5 x 10^9/l, and very severe aplastic anaemia with neutrophils lower than 0.2 x 10^9/l.[7]
The aetiology of acquired aplastic anaemia is very diverse. Aplastic anaemia usually occurs without a suggestive prior history and is labelled idiopathic. However, in some cases a clear inciting event can be identified. Many drugs and chemicals have been described as causing aplastic anaemia by a rare idiosyncratic reaction. The most well known are drugs such as chloramphenicol, but widely used medications as furosemide and allopurinol have also been associated with aplastic anaemia.[8]
Approximately 5 to 10% of aplastic anaemia occurs after an episode of hepatitis in which no known viral pathogen or a relation with drugs can be identified.[9] Patients who receive a liver transplantation for hepatic failure caused by such a seronegative fulminant hepatitis are at a high risk of developing aplastic anaemia. It occurs in about 25% of these patients.[10] It is plausible that a not yet identified infectious agent is involved. Also parvovirus B19 is associated with aplastic anaemia.[11]
Relationships with pregnancy[12] and autoimmune disorders such as eosinophilic fasciitis have also been reported. However, whatever the underlying cause, it does not seem to affect the response to treatment.[13]

PATHOGENESIS

There are several indications that aplastic anaemia is due to a stem cell dysfunction. When stem cells of patients are seeded onto irradiated normal stromal cells in vitro, a reduced number of colony-forming units (CFU) is seen. In contrast, normal CFU forming is observed after placement of normal CD34-positive cells into stromal cells of patients.[14] Therefore stromal dysfunction appears unlikely.

Furthermore, CD34-positive cells are decreased in blood and bone marrow,[15] while in the remaining stem cells an increased percentage of apoptotic cells is seen.[16]
Evidence is mounting that a T-cell-mediated reaction may be responsible for the stem cell destruction. In bone marrow of patients an increased number of activated CD8 lymphocytes are seen.[17] Moreover, T cells of patients are capable of reducing CFU forming in vitro, while depletion of these T cells restores CFU forming.[18] Furthermore, T cells of patients produce cytokines such as interferon-γ and tumour necrosis factor-α and increased expression of these cytokines has been shown in the bone marrow of patients.[19] These cytokines can suppress stem cell proliferation and induce apoptosis of stem cells.[20] The cytokine-induced apoptosis can occur directly and indirectly by the Fas-Fas-ligand system. Interferon-γ and tumour necrosis factor-α are capable of inducing Fas expression on stem cells, and increased Fas expression is found in bone marrow of patients.[21] Fas ligand, which can be found on activated T lymphocytes, can subsequently induce apoptosis of these Fas-expressing stem cells.
The important role of these cytokines is underscored by the observation that in a murine model of aplastic anaemia, pancytopenia can be ameliorated by treatment with antibodies against IFNγ.[22]
So, at present the hypothesis is that activated CD8 lymphocytes induce apoptosis of stem cells directly as well as by cytokines produced by these CD8 lymphocytes. However, the exact mechanisms inducing this immune reaction are unknown. Because there are so many diverse causes of aplastic anaemia, it can be assumed that there are also various mechanisms leading to T-cell activation. For instance, after a viral infection, molecular mimicry may be involved and in case of an idiosyncratic drug reaction, hapten forming. Recently, it was found that the P-glycoprotein function of stem cells was reduced in patients with drug-induced aplastic anaemia compared with patients with aplastic anaemia due to another cause.[23] This decreased function of P glycoprotein, which is involved in drug efflux, may lead to increased accumulation of drugs in stem cells and subsequently result in increased cytotoxicity in these cells. Therefore, patients with decreased P-glycoprotein function might be more prone to develop drug-induced aplastic anaemia.
In a subset of patients a mechanism other than immune-mediated stem cell damage may be involved. Recently, in some patients with aplastic anaemia a germ-line mutation in the gene encoding for the RNA component of telomerase has been shown.[24] This mutation results in decreased telomerase activity and subsequently shorter telomers, which may ultimately lead to reduced survival of stem cells and to aplastic anaemia.

TREATMENT

Allogeneic stem cell transplantation (allo-SCT) using bone marrow as treatment for aplastic anaemia was first applied in the early seventies. Nowadays, peripheral stem cells are being increasingly used. When successful, a fast haematological response is seen after allo-SCT with neutrophils above 0.5 x 10^9/l and platelets above 20 x 10^9/l after a median of about 15 and 20 days, respectively. However, allo-SCT can be accompanied with severe toxicity. The main mortality and morbidity is due to graft failure, drug-related toxicity, infections and the occurrence of acute and/or chronic graft-versus-host disease (GVHD). Recently the European Group for Blood and Marrow Transplantation (EBMT) retrospectively analysed the data of 2002 patients with aplastic anaemia who had received an allo-SCT between 1976 and 1998.[25] Most patients (85%) received a transplant from an HLA-identical sibling, 13% from a matched unrelated donor, and 2% from an identical twin. Graft type clearly affected survival in these three groups with 66, 37, and 91% respectively. Data on responses were not given.
Mortality was strongly associated with age. In patients treated with allo-SCT from an HLA-identical sibling between 1990 to 1998, survival rates for patients aged <16, between 16-40, and >40 years were 77, 68, and 54%, respectively. Remarkable was the improvement in time with an increase in survival from 57% up to 1990 to 76% after 1990. This improvement is mainly caused by a decline in the occurrence of acute GVHD due to more effective prophylaxis, better matching, and improved supportive care.
In patients who are not candidates for SCT, immunosuppressive therapy (IST) is employed. Mathe *et al.* reported autologous bone marrow recovery in some patients who rejected their grafts. These authors speculated that the antithymocyte globulin (ATG) used in the conditioning regimen had induced an anti-immune process.[26] Since then, several randomised studies have been carried out. Drugs studied in a randomised setting are ATG, cyclosporine A (CsA), androgens, corticosteroids, growth factors and cyclophosphamide (*table 2*). However, these trials are very difficult to compare due to differences in inclusion criteria, definitions for response, time of follow-up, and treatment regimens. Until now, the best results have been reported with the combination of ATG and CsA. Both horse and rabbit ATG are frequently used and both are licensed for treatment in the United States. Data comparing both types ATG and several doses are not available. In our centre, the combination treatment consists of horse ATG 15 mg/kg administrated daily for five days and CsA for at least three months. Initially, CsA is administered orally twice daily at 3 mg/kg. Dosing of CsA is adjusted to

Table 2

Results of trials comparing different regimens of IST for aplastic anaemia. Definitions for response rate and follow-up for survival differs between studies

AUTHOR	N	TREATMENT	RESPONSE RATE (%)	SURVIVAL (%)	REMARKS
Champlin[27]	21	ATG	52*	62	
	21	Control	0	62	
Camitta[28]	29	ATG	69*	76*	
	13	Control	23	31	
Champlin[29]	26	ATG/andr	42	55	
	27	ATG	44	50	
Doney[30]	12	mcAb	8	58	
	13	ATG	31	77	
Kaltwasser[31]	15	ATG/andr	73	87	
	15	ATG	31	43	
Frickhofen[32]	43	ATG/Mpr/CsA	65*	64	
	41	ATG/Mpr	39	58	
Gluckman[33]	48	ATG/Mpr	30	64	
	46	CsA	32	70	
Doney[34]	31	ATG/HD-Mpr/andr	48	47	
	33	ATG/LD-Mpr/andr	36	43	
Bacigalupo[35]	69	ATG/Mpr/andr	56*	71	
	65	ATG/Mpr	40	65	
Marsh[36]	54	ATG/CsA	74*	91	
	61	CsA	46	93	
Kojima[37]	35	ATG/CsA/andr/G-CSF	55	91	Study in children
	34	ATG/CsA/andr	77	93	
Tisdale[38]	15	CsA/cycloph	46	NR	Premarurely terminated; excess mortality in cyclophosphamide group
	16	ATG/CsA	75	NR	

*ATG = antithymocyte globulin, andr = androgen, mcAb = murine antihuman T cell monoclonal antibody, Mpr = methylprednisolone, CsA = cyclosporine A, HD-Mpr = high-dose methylprednisolone, LD-Mpr = low-dose methylprednisolone, cycloph = cyclophosphamide, NR = not reported. * Significant difference ($p<0.05$).*

maintain trough levels of 100 to 300 ng/ml from day 1 to 28; from day 28 target trough levels are 50 to 150 ng/ml. CsA can be tapered off when there is a good response, and if necessary, restarted in case of relapse. During administration of ATG, corticosteroids are given for attenuating ATG-induced side effects. The corticosteroids themselves probably have a minor effect in aplastic anaemia.[34]

Good responses by this combination treatment, defined as neutrophils above 1.0 x 10^9/l and transfusion independence, are obtained in 60 to 80% of the patients. These responses, however, are rather slow and usually take three to six months to occur. Furthermore the response is often not complete (normalisation of blood counts) and about 30 to 40% show a relapse after a few years. Over time, five-year survival has improved because of better supportive care. In 1981, the five-year survival was 58% compared with 75% in 1991.[39]

In case of relapse or nonresponding disease after a first course, a second course of IST can be given. This second course is successful in approximately 50% of the patients.[40] Concern for development of serum sickness by repeated courses of ATG was examined by Tichelli *et al.*[40] These authors showed that a repeated administration of horse ATG is safe and well tolerated. Serum sickness occurred earlier but not more often.[40] When disease is refractory to repeated courses of IST, an allo-SCT can be considered when the patient was not a candidate for primary treatment with SCT.

LONG-TERM EFFECTS

Because both allo-SCT and IST have rather good effects in the short term, long-term effects are important. About 10% of the patients treated with IST for aplastic anaemia develop paroxysmal nocturnal haemoglobinuria (PNH) with haemolytic anaemia.[41] This does not occur in patients treated with allo-SCT. PNH is due to a mutation in a gene encoding for a protein which is involved in the synthesis of a glycosylphosphatidylinositol anchor (GPI)

responsible for the attachment of several proteins to the cell membrane. PNH usually presents with haemolytic anaemia but in 20 to 50% of the cases of aplastic anaemia a decreased expression of GPI-anchored proteins is found suggesting a strong link between these two conditions.[42] PNH as a long-term side effect is only found in patients who initially present with aplastic anaemia combined with a decreased GPI-anchored protein expression.[42] An explanation for this increased incidence of PNH after IST could be that stem cell clones with decreased expression of GPI-anchored proteins have a growth advantage compared with normal stem cells in aplastic anaemia. Stem cells with GPI deficiency, which can also be found in normal people,[43] appear to be less prone to apoptosis than normal cells.[44] In a disorder like aplastic anaemia, in which apoptosis-induced stem cell damage is important, this phenomenon may subsequently lead to a growth advantage for these GPI-deficient cells and ultimately to PNH.

Socie *et al.*[45] compared the incidence of malignant tumours after treatment for aplastic anaemia. It was found that the number of cancers was clearly increased compared with the general population, especially the occurrence of acute leukaemia (115 times in patients treated with IST, 29 times in patients who received a transplantation). The incidence of the development of solid tumours was only significantly increased in patients who were treated with allo-SCT (5.7 times). Comparing both treatments, especially the occurrence of acute leukaemia and MDS was clearly increased in patients who were treated with IST compared with those who received allo-SCT. Altogether, this results in a cumulative ten-year incidence of all cancers of 18.8% in patients treated with IST and 3.1% in those who received an allo-SCT.[45] The strongly increased incidence of cancer in patients treated with IST is reflected in the survival curve which is still declining after a follow-up of five years, while the curve of patients treated with allo-SCT reaches a plateau after this time period.[46]

The reason for the strongly increased incidence of cancer is not exactly known. The incidence of solid cancer after transplantation is associated to the use of radiation in the conditioning regimen.[45] The strong increase of MDS in IST can be due to the fact that the initial diagnosis was not aplastic anaemia but hypocellular MDS. Another explanation could be that the remaining stem cells, not affected by the immune system, have an increased cell cycle to compensate for the damaged stem cells. The observed shortening of telomeres in peripheral leucocytes of patients is in agreement with this hypothesis.[47] The increased cell cycle results in an augmented number of mutations which may lead to either MDS or acute leukaemia. Other possible mechanisms described as being related to the increased AML/MDS incidence are multiple courses of ATG[45] and the use of G-CSF.[48]

BEST PRIMARY TREATMENT

An important remaining question is what the first-line therapy of a patient presenting with aplastic anaemia should be. Several studies comparing the efficacy of allo-SCT and IST have been performed (*table 3*). Again, these studies are difficult to compare. Most studies did not find a difference between these treatments, except for one study performed in children which showed an advantage for allo-SCT.[52] However, the number of patients studied in these trials was rather small.

Therefore, the European Blood and Marrow Transplantation Group (EBMT) retrospectively analysed data on 1765 patients with acquired aplastic anaemia.[40] Comparing both treatments, it appears that especially in younger patients up to 40 years with a strongly decreased number of neutrophils (<0.3 x 10^9/l), allo-SCT is the best treatment, while in patients older than 40 years IST gives the best results.[40] The advantage of transplantation compared with IST in younger, severely affected patients is probably due to a shorter time of improvement of blood counts which is especially favourable in those with a severe low number of neutrophils. The advantage for IST in older patients is probably caused by the increased mortality of allo-SCT in this group. However, the difference in advantage for IST in older patients decreases in time, probably

Table 3
Results of trials comparing IST with allo-SCT for the treatment of aplastic anaemia – follow-up for survival differs

		IST		ALLO-SCT	
AUTHOR	AGE (YEARS)	N	SURVIVAL (%)	N	SURVIVAL (%)
Speck[49]	All ages	32	69	18	44
Bayever[50]	<25	22	45	35	72
Halperin[51]	<18	12	25	14	79
Locasciulli[52]	<15	133	48	171	63*
Paquette[53]	Adults	146	49	55	72

IST = immunosuppressive therapy, allo-SCT = allogeneic stem cell transplantation. Significant difference (p<0.05).*

due to relapses and the increased incidence of cancer. In patients aged up to 40 years and with a moderately affected neutrophil number there is no clear difference in five-year survival in favour of either of the treatment options.[40] However, because of the increased long-term effects of IST compared with allo-SCT, the latter is to be preferred.
So, in our institute, this has accumulated in the protocol as depicted in *table 4*.

Table 4
First, second, and third-line therapy for aplastic anaemia in the Erasmus Medical Centre

NEUTROPHILS <0.2 x 10^9/l	NEUTROPHILS >0.2 x 10^9/l
Age <45 years	*Age <20 years*
1. sib-SCT	1. sib-SCT
2. IST	2. IST
3. MUD-SCT	3. MUD-SCT
Age ≥45 years:	*Age ≥20 years*
1. IST	1. IST
2. sib-SCT (<55 years)	2. sib-SCT (<55 years)
3. MUD-SCT (<50 years)	3. MUD-SCT (<50 years)

sib-SCT = allogeneic stem cell transplantation from HLA-identical sibling, IST = immunosuppressive therapy, MUD-SCT = allogeneic stem cell transplantation from matched unrelated donor.

CONCLUSION

During the last decades, insight in the pathogenesis of aplastic anaemia has increased. In parallel with this, the prognosis of this potentially fatal disorder has improved radically. It can be expected that responses to IST will probably continue to rise partly due to new drugs tested for their efficacy in aplastic anaemia, such as mycophenolate mofetil, rapamycin, and monoclonals against the interleukin-2 receptor. Also results of allo-SCT will probably improve by better supportive care, more effective GVHD prophylaxis and less toxic conditioning regimens. This improvement of treatments urges that recommendations for treating aplastic anaemia will continue to be defined.

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Predicting the need for hospital admission in patients with intentional drug overdose

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ABSTRACT

Background: Self-poisoned patients are often admitted to a medical unit. However, often no treatment is given. We have developed a model to predict those patients who will not be treated and how long patients should be observed before this prediction can be safely made.

Methods: In this retrospective study a model to predict treatment was developed based on cases of self-poisoning in 1996 and validated on cases between 1997 and 1999. In a teaching hospital in the Netherlands 299 adults performing 353 episodes of self-poisoning were studied. The main outcome measures were predicted versus initiated medical treatment, time to prediction and time to initiation of treatment.

Results: The model predicted that in 51% (156/307) of all autointoxications no treatment would be given. In 2% (6/307) of all cases, treatment was incorrectly not predicted. All but one of these were preventive treatments based on the ingested compound. 4.5 hours after admission no additional patients fulfilled the criteria for prediction of treatment and all treatments were started within 4.5 hours.

Conclusions: In 51% of patients that present with an autointoxication the model accurately predicts that no treatment will be initiated. This decision can be made in the first 4.5 hours after presentation. This model can be used for a first screening of patients. It can also be used as a basis for a further prospective study to establish rational guidelines in the management of these patients.

INTRODUCTION

In the developed world, self-poisoning accounts for thousands of admissions each year and its incidence is increasing. In the UK, around 10 to 15% of the workload in emergency departments[1] and medical units involves self-poisoning.[2]

Clinicians dealing with autointoxication are faced with two questions: 1) does or will the patient need medical treatment requiring hospitalisation, and 2) how long does the patient need to be observed before a decision not to admit the patient can be safely made?

The history of these patients may be unreliable.[3] Thus, it is often unclear at what time, what amount and what type of drug(s) have been ingested. Consequently, it is uncertain whether the clinical situation may be aggravated in the coming hours. For these reasons, many of these patients are admitted to a medical unit. However, in many cases no treatment is given and the patient is discharged the next morning. Admissions are not based on clear clinical criteria.[4] For patients admitted to the ICU it has been found that applying a simple list of clinical criteria could reduce the admission rate by 40%. [5] Until now, such an analysis has not been performed for patients admitted to a medical unit (department of internal medicine and intensive care).

We aimed to develop a list of clinical criteria to predict if a patient will need to receive treatment or not. Secondly, we aimed to determine the observation period that is necessary and sufficient to be able to make this prediction. If it is predicted that no treatment will be given, the patient can be referred to the psychiatrist for further care. Unnecessary admission to a medical unit should be avoided. The staff is not specifically trained to take care of

these patients, which may lead to inappropriate behaviour and neglect.[6,7] In view of current resource constraints the issue has become even more pressing.

MATERIALS AND METHODS

The records of all patients presenting to the teaching hospital between 1 January 1996 and 12 December 1999 because of self-poisoning were studied retrospectively. Therefore, this study was excluded from ethical review by the institutional review board. Adult patients (>17 years) were identified using the hospital information system. This system registers all patients seen in the hospital, including those who were not admitted after visiting the emergency department. Excluded were patients who were transferred to another hospital, and patients who had taken more than 3 g acetaminophen because there are clear guidelines for this intoxication.[8] Follow-up of patients not admitted in the hospital was obtained by telephone from their general practitioners. If follow-up was not available, the patient was excluded from analysis.

Based on existing literature[5] and expert opinion a list of clinical and laboratory parameters was developed to serve as a model to predict treatment. The list comprises basic clinical and laboratory parameters, and questions on medical history and ingestion of slow-release medication. These parameters were collected from the clinical charts in the period between presentation and the start of treatment or, if no treatment was started, between presentation and discharge. Only parameters that were available in the chart were used in the model. If any criterion on the list was met (so, if one or more of the criteria were present), the model predicted treatment.

Cut-off points were based on the records of patients who were admitted to the internal medical ward in 1996 (reference group), in such a way that >95% of treatments were predicted by the list. The model was validated on patients seen between 1997 and 1999. It was determined whether any of the criteria that predicted treatment were met and if so, at what time after admission. Prediction of treatment was compared with actual initiation of treatment in these patients. Treatments were any medical actions that required hospitalisation (fluid administration, oxygen delivery, etc.) except for fluid administration of less than one litre per 24 hours. Moreover, the number of hours after presentation before treatment was started was recorded.

RESULTS

Using the hospital information system episodes of self-poisoning were identified during the reference period 1996 (admitted to the internal medical ward) and the validation period (1997 to 1999). The reference group consisted of 40 episodes of self-poisoning in 37 patients. The validation group consisted of 436 episodes of self-poisoning. From 32 episodes, clinical records could not be found and 97 episodes were excluded (38 because of transfer to another hospital, 53 because of ingestion of acetaminophen and 6 were lost for follow-up). This yielded 307 cases of self-poisoning in 254 patients in the validation group. Of these, 185 were admitted to a medical unit (62 to the ICU and 123 to the internal medical ward) and 122 to the psychiatric ward or sent home. None of the patients died or had sequelae of the autointoxication.

Table 1 shows the group of drugs and compounds that patients reported to have ingested. One has to realise that this list is based on the history of the patient, which may be unreliable, and not on toxicological analysis. The kinds of drugs reported are similar to what has been published in the literature.[9] No differences were found between amount and prevalence of drugs taken in patients admitted to a medical unit and other patients (i.e. patients admitted to the psychiatric ward and patients who were sent home; data not shown). As expected, benzodiazepines were most frequently used and in the group admitted to the ICU there was a higher prevalence of ingestion of tricyclic antidepressants (data not shown).[10]

Table 1
Drugs ingested in 307 episodes of self-poisoning in 256 patients (1997-1999)

DRUG CATEGORY	N (%)[A]
Benzodiazepines	197 (64%)
SSRIs[B]	51 (17%)
NSAIDs[C]	35 (11%)
TCAs[D]	34 (11%)
Phenothiazines	33 (11%)
Opioids	21 (7%)
Antipsychotics	19 (6%)
Antiepileptics	15 (5%)

[A] Number (%) of autointoxications in which patients reported to have taken a drug of this category. [B] SSRIs = Selective serotonine reuptake inhibitors. [C] NSAIDs = Non-steroidal anti-inflammatory drugs. [D] TCAs = Tricyclic antidepressants.

In *table 2* the list of criteria used to predict treatment is presented. Predicted versus actual treatment in patients seen in the period 1997 to 1999 is presented in *table 3*. The sensitivity of the model to predict treatment is 92%, whereas the specificity is 65%. In the upper panel of this table it can be seen that in 156 out of 307 episodes of self-poisoning (51%) the model predicts that no treatment will be given. In six cases this prediction was incorrect, so the

Table 2
List of criteria: if any of these criteria is met, the model predicts treatment

Medical history	History of diabetes mellitus/epileptic fits/cardiovascular disease/lung disease
Rectal temperature	<36 or >38.4°C
Mean blood pressure	<70 mmHg
Heart rate	<60 or >109 beats/min
Respiratory rate	<12 or >24/min
Oxygenation	PO_2 ≤9.3 kPa
Arterial pH	<7.33 or >7.49
Serum sodium	<130 or >149 mmol/l
Serum potassium	<3.5 or >5.4 mmol/l
Serum creatinine	>110 μmol/l
QRS duration	>0.10 s
QTc time	>0.44 s
Responds to talking	No
Epileptic fits	Yes
Ingestion of a slow-release drug or caustic agents?	Yes

Table 3
Prediction versus actual commencement of treatment in patients presenting because of self-poisoning in 1997-1999: treatment is predicted if any of the criteria listed in table 2 are met

All self-poisonings occurring in 1997-1999		*Treatment given?* *Yes*	*No*	Total
Treatment predicted?	*Yes*	70	81	151
	No	6	150	156
	Total	76	231	307
Self-poisonings admitted to the medical unit in 1997-1999		*Treatment given?* *Yes*	*No*	Total
Treatment predicted?	*Yes*	70	58	128
	No	6	51	57
	Total	76	109	185

negative predictive power of the model is 96%. Four of these patients were treated preventively with forced diuresis (three because of reported ingestion of NSAIDs and one of lithium). One was treated with naloxone because of mild heroin intoxication and one was treated with saline without obvious reasons.
In 151 episodes the model predicts treatment, whereas treatment was actually given in 70 of these, yielding a positive predictive power of 46%. In 23 episodes the patient was not admitted to the medical unit, despite the fact that treatment was predicted (data not shown). No sequelae occurred in any of these patients.

As stated, the model predicts treatment in 151 auto-intoxications, whereas there were 185 instances of admission to a medical unit. So use of this model could lead to a small reduction of admissions. If the model were to be applied to patients admitted to a medical unit only, in 57 out of 185 episodes it predicted that treatment would not be given (table 3, lower panel).
In 148 out of 151 predicted treatments, the criteria were met within the first hour after presentation. In three of them, criteria were met at a later time point, 4.5 hours after presentation at the latest. The time until a criterion is met can roughly be considered to be (negatively) exponentially distributed. Taking the probability that the criterion is met after 4.5 hours (or later) to be one in 151, it can be calculated that the probability that a criterion is met more than six hours after presentation is 0.12%.
In 76 cases the patient was treated: in 71 of these, treatment was started within the first hour of presentation and the maximum time before treatment was commenced was 4.5 hours. Following the reasoning described above, the probability a treatment will be initiated more than six hours after presentation is 0.32%.

DISCUSSION

The decision whether or not to admit a patient after self-poisoning is based on a combination of the history (how much of what drug was ingested and when) and the clinical parameters. However, every clinician realises that the history may be unreliable[3] and the clinical picture may alter in time. For that reason many of these patients are admitted to a medical unit, even if they are in no physical distress. In the majority of these patients the clinical course is benign and no treatment is given. Because of the unreliability of the history we developed a list of criteria that is mainly based on the clinical condition of the patient. This list of criteria has to be applied on the clinical and laboratory parameters that the clinician finds relevant to collect in a specific patient. Since the patient's condition may alter in time, we studied all data collected after presentation until treatment was started or until discharge. We reasoned that admission to a medical unit was not justified if no treatment was given. Because of the retrospective nature of our study, we were not able to judge whether a treatment that had been given was necessary or not. So, we set up a model to predict non-treatment: if treatment is not given, it is clear that admission for medical reasons is not necessary and the psychiatrist may decide whether to admit a patient for psychiatric or social reasons. Administration of less than 1 litre of fluid intravenously per 24 hours was not considered a treatment justifying admission. This has no substantial effect on the circulation and is only given to ensure quick access to the circulation.

Using the list of criteria in patients admitted to the medical unit, a considerable number of patients could be identified who, during six hours of observation, did not meet any of the predictive criteria. The negative predictive power of our model is high (96%), so using this model one can decide not to admit these patients. The positive predictive power of the model is low, so if the model predicts treatment this does not necessarily mean that this treatment will be given. Thus, this model could be used as a first screening to decide who should not be admitted to a medical unit. If the model predicts treatment, the clinician should decide, depending on the particular case, if admission is necessary. For instance, although a patient with non-insulin dependent diabetes mellitus (NIDDM) meets a criterion that predicts treatment, that does not mean that every patient with NIDDM should be admitted after an autointoxication. There were some patients who were treated although this was not predicted. All but one of these were treated preventively, based on the history of the ingested compound. These cases show that it is impossible to completely ignore the history.

In some patients who were not admitted, criteria were found that predicted treatment. In these patients treatment was not started. Some of them were even sent home. No clinical problems were reported in these patients. This again shows that if a treatment is predicted, it does not mean that this treatment is necessary. We do not think that all of these patients should be admitted. Our criteria list could be used to identify patients who will not be treated and therefore should not be admitted to a medical unit. An observation period of six hours is enough to make this decision. The psychiatrist should make further decisions in these patients. Admission to a medical unit should be considered, but is not obligatory, in all other patients.

Since this is a retrospective analysis, our study has a few drawbacks. We only used data that were available in the charts. These were the parameters the attending physician felt necessary to be able to judge the severity of the auto-intoxication. For instance, if a patient is not in respiratory distress, no blood gas analysis will be performed. So we felt it is justified to use only parameters that were available in the charts. We feel, however, that this model should be further validated and for this reason we are currently planning a prospective study. We expect that this will lead to guidelines regarding which patients should be admitted to the medical unit and who should be referred to the psychiatrist to decide whether the patient can be sent home.

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Intoxication with therapeutic and illicit drug substances and hospital admission to a Dutch University Hospital

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ABSTRACT

Background: This article describes the retrospective analysis of the patients who presented with a drug-related intoxication to the emergency department of the Erasmus Medical Centre in 2000.

Methods: Data were collected from the emergency department's electronic database and the medical charts of the patients.

Results: A total of 243 patients were seen with a drug-related intoxication caused by ingestion of one or more medical substances, drugs of abuse (DOA) or combinations with alcohol. Mono-intoxication occurred in 58% of the patients, predominantly caused by DOA (56 patients), analgesics (17 patients) or benzodiazepines (14 patients). Benzodiazepines (55 patients), analgesics (42 patients), alcohol (42 patients), DOA (40 patients) and antidepressants (23 patients) were predominant in combined intoxications. More than half of the patients (142) were discharged after being treated in the emergency department and 80 patients were admitted to the wards. Eighteen patients were admitted elsewhere and three patients were lost to follow-up. Eventually, 70 patients were discharged after having been admitted, five patients were admitted to other institutions, two patients died and three patients were lost to follow-up.

Conclusions: DOA, benzodiazepines, analgesics, alcohol and antidepressants accounted for approximately 65% of the drug-related intoxications in 2000 and in a third of the presenting patients, toxicity was such that admission to the wards was warranted.

INTRODUCTION

Several papers in the international literature have dealt with drug-related intoxication, in some cases in relation to hospital admission.[1-7] Intoxication with medical substances or drugs of abuse (DOA) accounts for approximately 1% of the patients who present to emergency departments.[1,5] Although there are differences between countries, DOA, analgesics, antidepressants, anxiolytics, and sedatives are the most frequently occurring substances in case of (auto)intoxication.[1,6] In the Dutch medical literature, several case reports have been described regarding a broad range of intoxications. Furthermore, there have been a small number of studies outlining the relationship between intoxication with specific substances and hospital admission[8,9] as well as the topic of intoxication in children.[10] However, more comprehensive studies on the topic of drug-related intoxication seen in an emergency department and the relationship with hospital admission are lacking. The Erasmus Medical Centre is a large university hospital complex. The hospital complex has a capacity of approximately 1240 beds, divided over three locations.
This article describes the results of the retrospective analysis of the patients who were seen in the central emergency

department of the Erasmus Medical Centre in 2000. The focus is particularly on the role of medical substances, follow-up of the patients and final outcome. Furthermore, this study aims to compare data from literature on drug-related intoxication with the specific situation at a large Dutch university hospital.

MATERIALS AND METHODS

The time frame of this study was 1 January to 31 December 2000. An admission database is maintained electronically in the central emergency department of the Erasmus Medical Centre of all presenting patients. Recorded data included demographic status, reason for presentation (i.e. nature of the intoxication, whether or not the intoxication was a suicide attempt, which substances were involved) and outcome. Our study is based on data extracted from this database, combined with data from the patients' medical records. The patients seen in the emergency department of the Sophia Children's Hospital are not included in this analysis.
The locations to which the patients were discharged from the emergency department were collected from the automated hospital system and a specific database maintained at the intensive care unit (ICU) for internal medicine. Unfortunately, due to the way laboratory results are documented in the automated hospital system, it is not possible to identify the specific lab tests that are carried out as part of the medical care of patients who present to the central emergency department of the Erasmus Medical Centre. Consequently, the analysis performed in this study is based on the electronic admission database of the emergency department and not on toxicological analysis.

RESULTS

In 2000 a total of 576 patients presented to the central emergency department of the Erasmus Medical Centre with the indication 'intoxication', accounting for 2.4% of all presentations (23,995 patients) (*figure 1*).
Fifty-eight percent of these cases (333 patients) were due to mono-intoxications (intoxication with only one substance) involving alcohol (277 patients; 213 males, 64 females), carbon monoxide (27 patients; 14 males, 13 females), chemicals (one male patient) or unknown substances (28 patients). In the remaining 243 cases, intoxication was

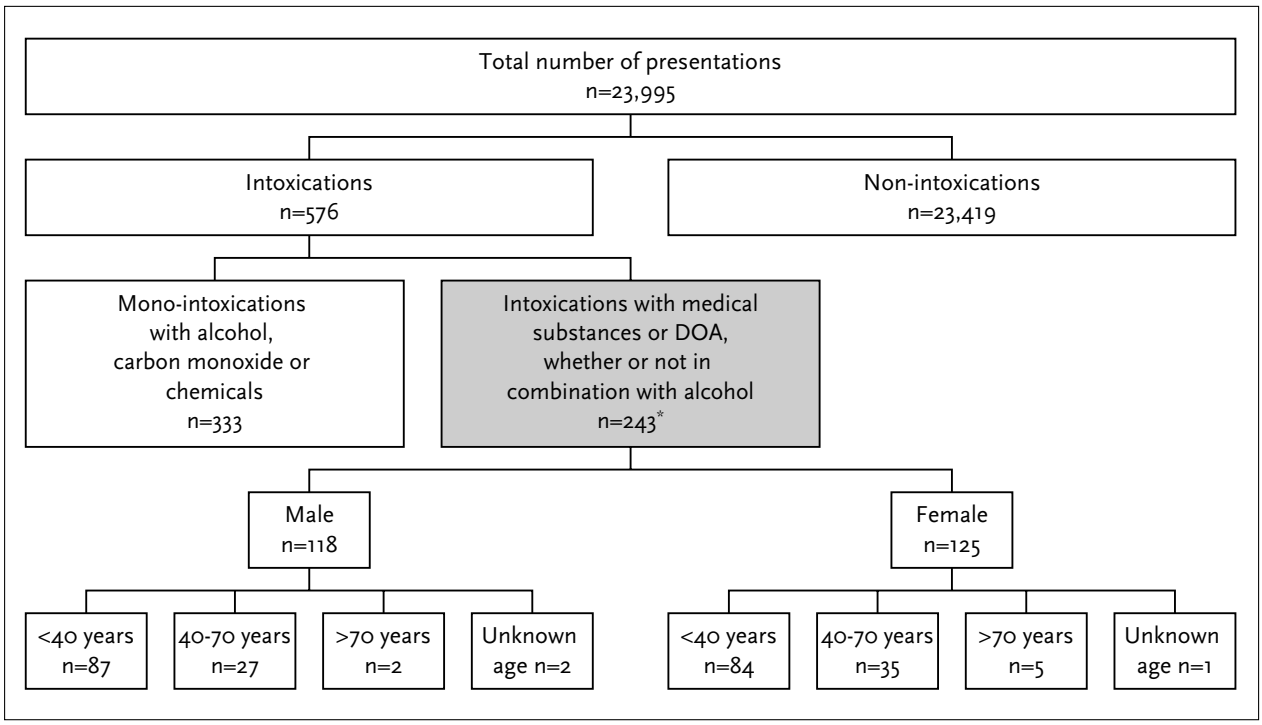

Figure 1
The caseload presenting to the central emergency department of the Erasmus Medical Centre in 2000
* **The analysed population, DOA = drugs of abuse.**

due to one or more medical substances or DOA (including recreational drugs such as 'XTC'), and combinations thereof with alcohol. The patients who presented with a mono-intoxication with alcohol, carbon monoxide or chemicals have been excluded from the analysis because the primary focus of this study was on drug-related intoxication.
There are no significant differences in sex distribution of the analysed patients but there is an uneven age distribution of the patients (*figure 1*). Over 70% of the patients were below the age of 40 (171 patients).
Intoxication with a single substance occurred in 140 of the 243 studied patients (*figure 2*). The other patients used combinations of two (57 patients), three (14 patients), four (13 patients), five (five patients) or six (one patient) drugs, and in 13 cases the cause of the intoxication was unknown. The drugs most frequently involved in cases of combined intoxication are shown in *figure 3*.
Nearly 60% of the patients were discharged home after presentation to the emergency department (142 patients). A total of 80 patients were admitted to the wards (*figure 4*). Fifteen patients were admitted elsewhere (i.e. police station, Salvation Army) and three patients were treated outside the Erasmus Medical Centre (crisis centre, psychiatric hospital). The necessary data are missing for the remaining three patients.
The patients who were discharged home were significantly younger than patients admitted to the Erasmus Medical Centre (mean age: 32.5 years and 40.5 years for patients discharged home and admitted, respectively; $p<0.05$; student's T test). There were no age differences between males and females within both of these groups (discharged: males 33.2 years, females 31.6 years; admitted: males 39.6 years, females 41.1 years). Furthermore, more females were admitted (33 males, 47 females), whereas more males were discharged home (76 males, 66 females).
Eventually, 86% of the patients who had been admitted to the wards of the Erasmus Medical Centre were discharged home (70 patients), five patients were referred to other institutions, two patients died and three patients were lost to follow-up. The mean duration of stay on the wards was 4.5 days (SD = 7.8 days, range = 1-45 days, median = 2 days).
One of the deceased patients was an 88-year-old male who attempted suicide due to the poor prognosis of a disseminated solid tumour. The other patient who died was a 32-year-old woman who attempted suicide with unknown substances. The patient suffered from renal failure due to extensive misuse of drugs in her medical history and refused haemodialysis.

DISCUSSION

The results of this study show that approximately 1% of the patients presenting to the central emergency department of the Erasmus Medical Centre have intoxications from medical substances or DOA and combinations thereof

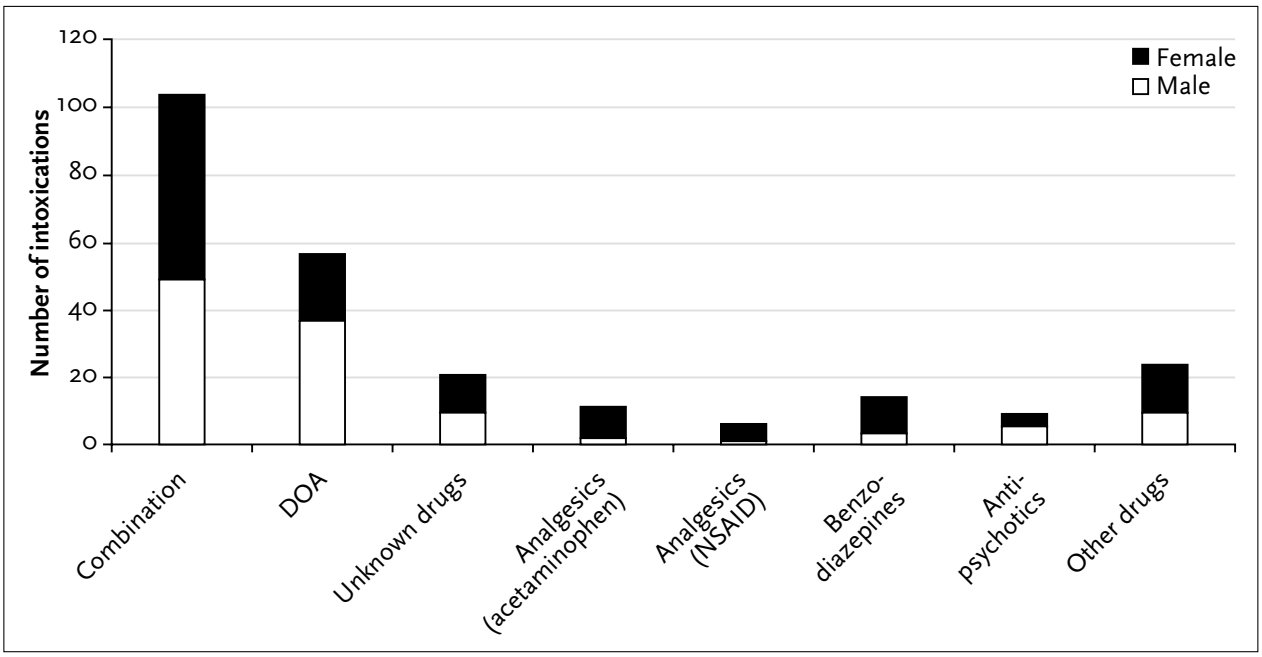

Figure 2
The investigated population categorised by involved substance
DOA = drugs of abuse, other drugs = <4 presentations/category, including antidepressants, antihistamines, antibiotics, antiepileptics, anticoagulants, β-blockers, calcium channel blockers, antineoplastic drugs, digoxin, hypnotics, lithium, parasympathomimetics, and vitamins.

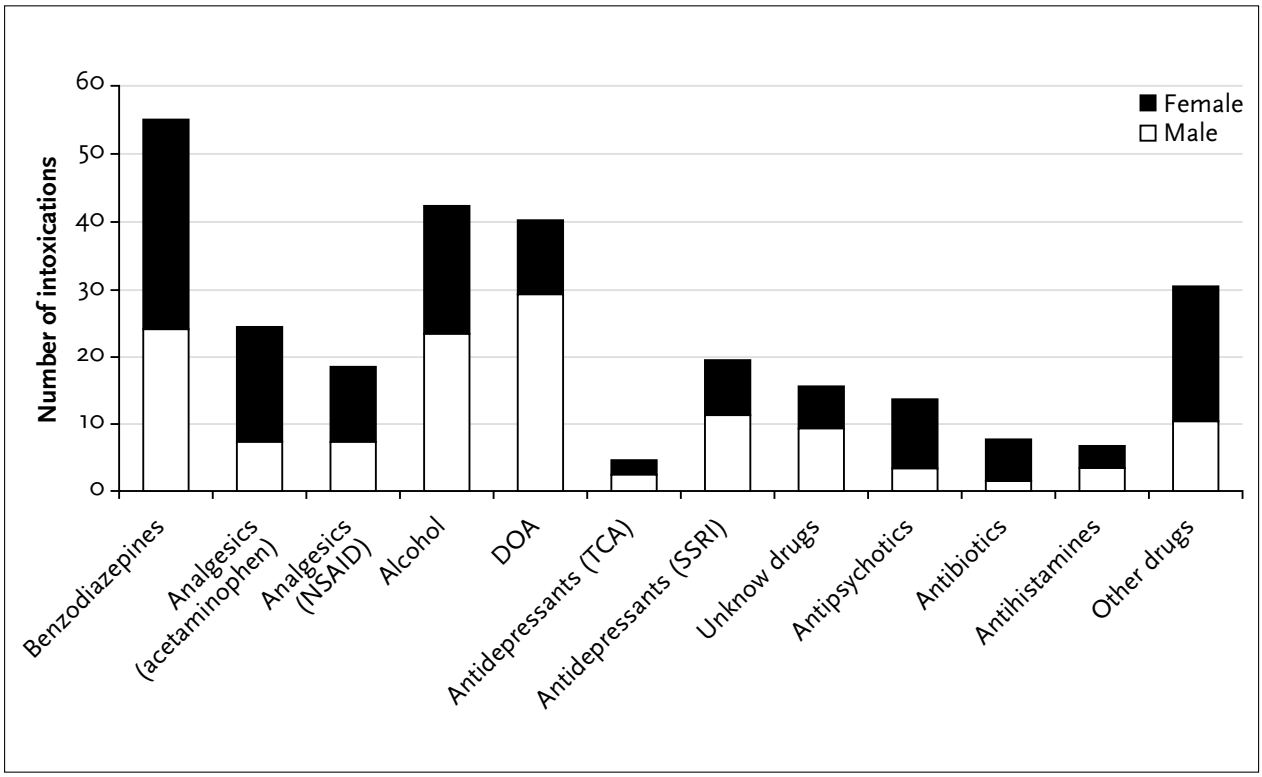

Figure 3

Categorisation of the patients with a combined intoxication by involved substance

DOA = drugs of abuse, other drugs = <4 presentations/category, including ACE inhibitors, antiemetics, antiepileptics, anticoagulants, β-blockers, calcium channel blockers, folic acid, hormonal substances, lithium, nitrates, parasympathomimetics, proton pump inhibitors, iron and vitamins.

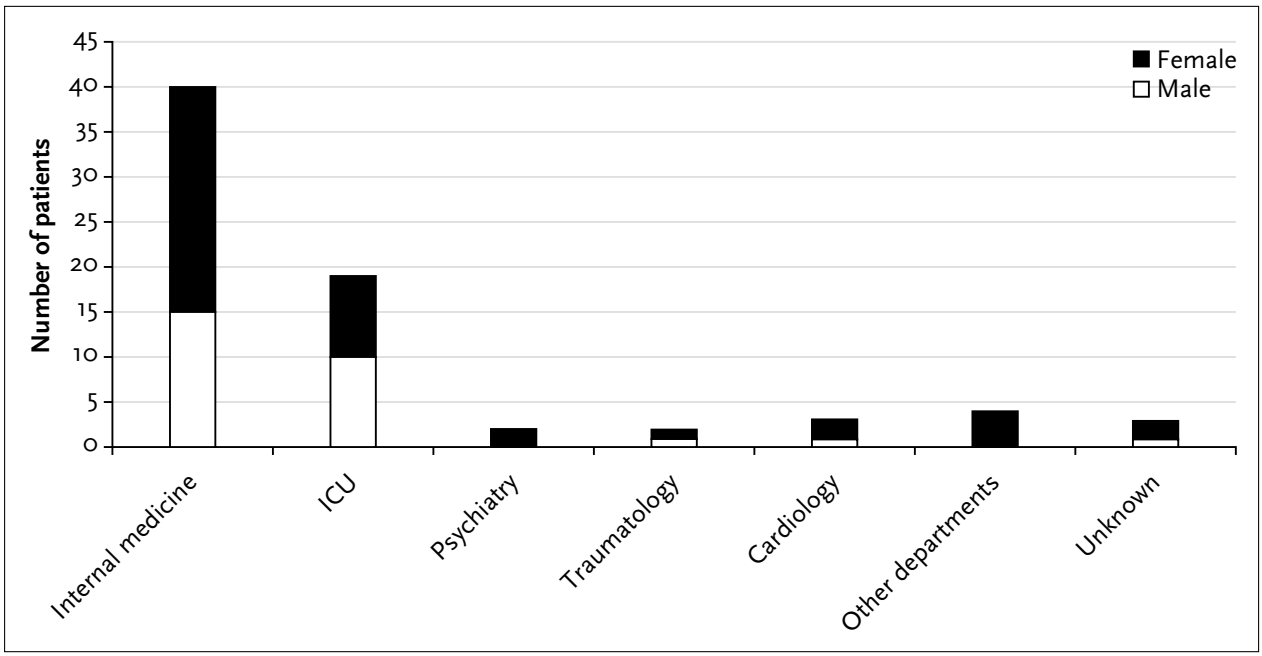

Figure 4

Categorisation of the patients who were admitted to the in-patient facilities of the Erasmus Medical Centre by involved department

Intensive care unit (ICU) = ICU internal medicine (19 patients), ICU surgery (5 patients) and ICU neurology (2 patients). Other departments = one patient admitted to each of the departments of neurology, geriatrics, general medicine and gastroenterology.

with alcohol. Over 40% of the patients had ingested a combination of substances and in 65% of the cases DOA, benzodiazepines, analgesics, alcohol or antidepressants were involved.
Strikingly, during the study period no mono-intoxications with antidepressants were seen in the emergency department. In the group of combined intoxications, antidepressants ranked five, after benzodiazepines, analgesics, alcohol, and DOA.
Our findings are in line with those from other studies regarding the percentage that intoxications account for in the total number of patients presenting to an emergency department (approximately 1%).[1,5] Of our patients, 33% were admitted to the hospital wards, which is consistent with data from literature (24 to 86.5%).[1,2,5] Despite the differences between countries, in most reported studies analgesics, antidepressants, anxiolytics and sedatives account for the majority of drugs involved in (auto)intoxications, which is consistent with our findings.[1,6]
After presentation and in some cases treatment in the emergency department, more than half of the patients were discharged home, a third of the patients were admitted to the wards and the remaining patients were referred to other institutions. Patients who were discharged home were significantly younger than patients who were admitted. Furthermore, relatively more females were admitted, whereas more males were discharged home.
A shortcoming in this study is the fact that the majority of the presented data were not obtained from toxicological analysis but from an electronic admission database, which is less reliable. Furthermore, follow-up is not complete as data on the undertaken action after presentation as well as after admittance to the hospital are lacking (three patients in both cases).
It can be concluded from this study that DOA, benzodiazepines, analgesics, alcohol and antidepressants were involved in approximately 65% of the drug-related intoxications seen at the central emergency department of the Erasmus Medical Centre in 2000. More than half of the patients were discharged home from the emergency department, while in a third of the patients the toxicity was such that admission to the wards of the Erasmus Medical Centre was warranted. The remaining patients were referred to other institutions or the exact follow-up could not be constructed due to a lack of information.

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NOTE

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Oblivion at the kitchen table

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CASE REPORT

A 44-year-old man presented at the emergency department with cutaneous eruptions. He was a former drug addict treated for hepatitis C infection in a clinical trial with interferon-alpha and ribaverine. He admitted having taken methadone the day before admission, but he was unable to tell us what had happened after ingestion. He woke up at the kitchen table some time during the night and went to bed. A few hours later he woke up again feeling very ill and noticing he was unable to walk. In the emergency department we saw a very ill man with extensive cutaneous eruptions: bullae, erythema and ulcerations with oedema on his right eyebrow, nose, right elbow and right arm and in the groins on both sides. His feet were swollen and large bullae were present on the dorsum of both feet as well as at the ankles (photographs). He was not febrile at admission but developed fever within hours. Laboratory results revealed a C reactive protein of 39 mg/l, leucocytes 9.2 x 10^9/l, creatinine of 162 μmol/l and a metabolic acidosis. The urine dipstick was positive for red blood cells but none were seen in the sediment.

WHAT IS YOUR DIAGNOSIS?

See page 182 for the answer to the photo quiz.

Photographs are shown with permission of the patient.

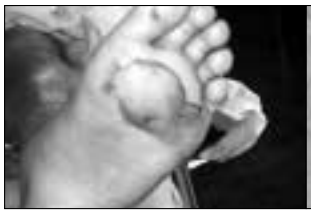

Figure 1

Figure 2

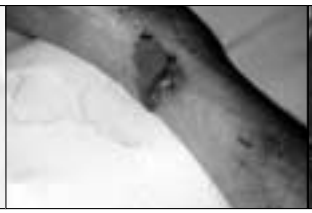

Figure 3

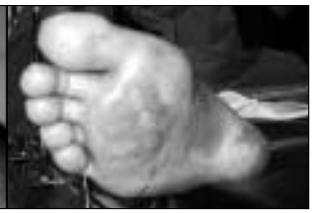

Figure 4

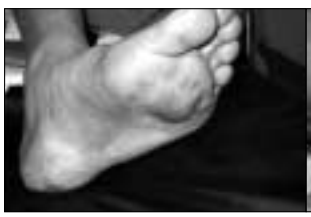

Figure 5

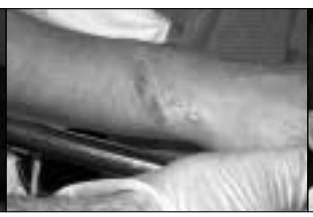

Figure 6

Figure 7

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CASE REPORT

A rare cause of haemolytic anaemia: paroxysmal nocturnal haemoglobinuria in an elderly patient

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ABSTRACT

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired haemopoietic stem cell disorder characterised clinically by chronic haemolytic anaemia with acute episodes, thrombosis and bone marrow failure. It is a rare condition, which usually occurs in younger people. Immunophenotyping and flow cytometry play a key role in diagnosing PNH. Treatment is mainly supportive. Because it is so rare, delay in diagnosis is not uncommon in patients with PNH, which has a considerable impact on patient management and prognosis.
We present this case to draw attention to this rare cause of haemolytic anaemia, which should be considered in any patient, of any age, who has signs of chronic haemolysis.

INTRODUCTION

Paroxysmal nocturnal haemoglobinuria, also known as the Marchiafava-Micheli syndrome, is an uncommon acquired clonal disorder characterised by chronic haemolysis with acute exacerbations, cytopenias of varying extent and a tendency to venous thrombosis.[1-3] It is associated with a somatic mutation in the PIG-A gene of a totipotent haemopoietic stem cell causing the blood cells of the PNH clone to be deficient in glycosyl phosphatidyl inositol anchored membrane proteins. Deficiency of these proteins leads to an increased sensitivity of PNH cells to complement-mediated lysis, which is responsible for chronic intravascular haemolysis and probably also for thrombosis.[3-5] The haemolysis usually occurs at night, although not in all patients. The reasons for this nightly occurrence are unclear but a lowering of blood pH at night may play a role. There is a close relation to aplastic anaemia and PNH may convert into acute leukaemia.[6-8] PNH usually occurs in young adults. In the present case, we report a Caucasian woman of older age with haemolytic anaemia in whom PNH was diagnosed.

CASE REPORT

A 67-year-old Caucasian woman presented with a history of progressive fatigue, dizziness and presumed haematuria, for which she had already seen a urologist who diagnosed an asymptomatic urinary tract infection. Her medical history revealed hysterectomy, angina pectoris and a frozen shoulder. Her mother died of chronic leukaemia at the age of 80. Her medication consisted of nitrofurantoin, ramipril and celiprolol. Physical examination showed a pale, tired-looking woman with normal blood pressure, pulse and temperature. No pathological lymph nodes were found. Heart, lungs and abdomen revealed no abnormalities. She had vitiligo over the upper extremities. The ECG and chest X-ray were both normal.
Laboratory tests showed the following results: ESR 31 mm/h (N. 2-20), haemoglobin 5.4 mmol/l (N. 7.5-10.5), Ht 0.27 l/l (N. 0.36-0.50), MCV 101 fl (N. 82-100), leucocytes 4.7 x 10^9/l (N. 4.0-10.0), platelet count 154 x 10^9/l (N. 130-340), haptoglobin <0.1 mmol/l (N. 0.28-2.00), LDH 8609 U/l (N. <450), bilirubin 36 µmol/l (N. <17), serum iron 15 µmol/l (N. 10-30) and reticulocyte count 70% (N. 0.7-2.4). Urine analysis showed haemoglobin and haemosiderin. Apparently, the patient was suffering from intravascular

haemolysis. A direct Coombs' test was negative. The blood smear showed no spherocytes, elliptocytes or fragmentocytes. Erythrocyte enzymes, such as G-6-PD, were normal as was haemoglobin electrophoresis. The following step in Coombs-negative haemolysis is the Ham's test and sucrose haemolysis test. Both these tests can confirm haemolysis in red cells of a patient's serum by activating complement, the first by lowering serum pH and the second by reducing ionic strength. The Ham's test was positive in our patient. To confirm the diagnosis, flow cytometry was then performed, which provided immunological evidence for the existence of PNH in our patient. This test uses monoclonal antibodies against phosphatidyl inositol (PI) anchored proteins on granulocytes, which under normal circumstances protect cells against complement-mediated lysis. In PNH, expression of these proteins is significantly reduced or absent, as in our patient, causing lysis of red cells.

Our patient was treated with blood transfusion, and iron and folic acid suppletion. In addition, we started with acenocoumarol as a prophylaxis against thrombosis which, after infections, is the main cause of death in patients with PNH. Our patient was readmitted after six months for another transfusion but is doing very well at the moment.

DISCUSSION

We present here a case of PNH in a 67-year-old woman. There was a delay in diagnosis because her haemoglobinuria was first thought to be haematuria. Doctors tend to overlook the diagnosis of PNH in patients with chronic haemolysis. Our patient was remarkable because of her age at presentation. Most patients diagnosed with this condition are young adults, the main symptoms usually first appearing in the third and fourth decades of life.[9]

The clinical course of PNH is highly variable, ranging from a mild defect to a lethal process. As previously stated, the main clinical features consist of haemoglobinuria, episodic haemolysis, marrow hypoplasia and thrombotic disease.[1-3] Renal failure occurs rarely in PNH.[10] There is a close relation to aplastic anaemia and conversion into acute leukaemia occurs in 5 to 15% of all patients.[6-8] PNH should

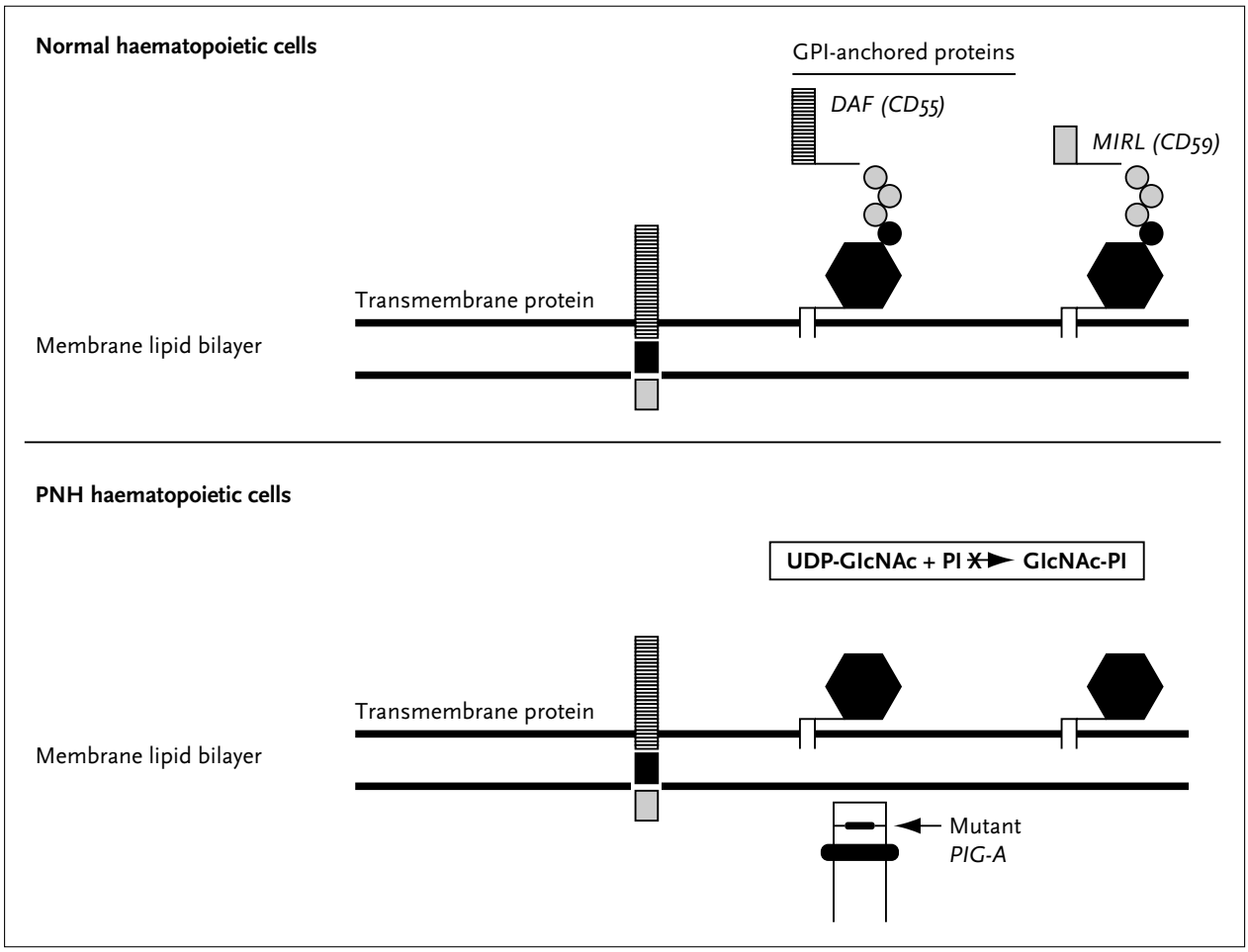

Figure 1
Normal and PNH haemotopoietic cells

be considered a very serious disease, the complications of which can be fatal. Nowadays, however, even mild cases can be detected because of new techniques such as flow cytometry, which is a specific diagnostic test for PNH.[11] In PNH, expression of PI-anchored proteins is significantly reduced or absent due to a mutation of the PIG-A gene, causing absence of PI-anchored proteins. In normal circumstances these proteins protect against complement-mediated lysis of red cells (*figure 1*). Flow cytometric analysis can exactly measure the expression of antigens on each cell membrane and estimate the percentage of deficient cells by using monoclonal antibodies. In our patient, only 5% of the granulocytes reacted with CD59, CD24 and CD16 antibodies, which recognise PI-anchored proteins. Erythrocytes of PNH patients are most deficient for DAF (CD55), MIRL (CD59) and AchE (CLBgran/5Ag).

PNH must be differentiated from antibody-mediated haemolytic anaemias (AIHA), especially paroxysmal cold haemoglobinuria and the cold agglutinin syndrome. This was done in our patient by performing a direct Coombs' test, which was negative. Warm and cold antibodies were also negative. Other causes of chronic haemolysis, such as corpuscular defects, were ruled out as well. Molecular analysis of haemoglobin showed no abnormalities. Erythrocyte enzyme values were normal.

With the exception of bone marrow transplantation, there is no curative therapy available.[12] Treatment depends on the clinical picture and consists of supportive measures, such as transfusion, antibiotics and anticoagulants.[1,2] Thrombosis occurs frequently and accounts for 50% of all deaths in PNH. Beneficial effects of steroids and splenectomy have been reported. We describe a patient with chronic haemolytic anaemia caused by PNH, which was diagnosed by flow cytometry. She was treated with blood transfusions, iron and folic acid suppletion, and a prophylaxis against thrombotic complications.

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CASE REPORT

Severe rhabdomyolysis and acute renal failure following recent Coxsackie B virus infection

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ABSTRACT

Viral infections have been associated with a wide spectrum of muscle disorders, ranging from acute nonspecific myalgia to myositis. However, severe rhabdomyolysis, with or without accompanying acute renal failure (ARF), has been described only rarely. We report the fourth case in the literature of recent Coxsackie B virus infection complicated by severe rhabdomyolysis and ARF, necessitating temporary haemodialysis in a previously healthy young man. Although most Coxsackie B virus infections are asymptomatic, one should be aware of this potentially life-threatening complication of this virus. As illustrated with the present case, serological testing may reveal the diagnosis in a case of rhabdomyolysis after a viral illness.

INTRODUCTION

Coxsackieviruses (group A and B) are RNA viruses and, together with polioviruses and enteric cytopathogenic human orphan (ECHO)viruses, are classified as *Enteroviruses*. They are a genus of the picornaviridae and are widespread throughout the world.[1] Although asymptomatic infection is common, there are at least six serotypes of Coxsackie B viruses which in neonates and young children predominantly affect the central nervous system and muscles causing potentially severe complications such as aseptic meningitis, encephalitis, myositis and myocarditis.[2,3] In older children and adults, Coxsackie B virus infections tend to be less severe.[1,2] However, Coxsackievirus-induced rhabdomyolysis has been described in rare cases.[4]

We report the fourth case in the literature of recent Coxsackie B virus infection complicated by severe rhabdomyolysis and acute renal failure in a previously healthy young man.

CASE REPORT

A previously healthy 32-year-old man was admitted to our hospital because of severe muscular pain, especially of the upper legs, and discoloured coca cola-like urine. He had a five-day history of malaise, sore throat, fever up to 40°C and headache. There was no family history of renal or musculoskeletal disease nor had he experienced any trauma, drug abuse or vigorous exercise. On physical examination we found a moderately ill patient with a blood pressure of 130/90 mmHg, pulse rate of 90 beats/min and a temperature of 37.5°C. Examination of lungs, heart and abdomen were normal but he had markedly swollen and tender calves and upper legs. There were no signs of myopathy.

Relevant laboratory values included a creatine phosphokinase level of 250,000 U/l (normal [N] 50-120), aspartate aminotransferase 1310 U/l (N. 0-30), alanine aminotransferase 320 U/l (N. 1-30) and lactate dehydrogenase 14,160 U/l (N. 100-320 U/l), consistent with skeletal muscle necrosis. The white blood cell count was 15.5 x 10^9/l (N. 4-10) with 13.2 x 10^9 granulocytes in the differential count and a platelet count of 419 x 10^9/l (N.150-400). Serum creatinine on admission amounted to 273 µmol/l (N. 75-110), urea 15.4 mmol/l (N. 2.5-7.5), sodium 138 mmol/l (N. 138-142), potassium 4.9 mmol/l (N. 3.5-5), calcium 2.38 mmol/l (N. 2.2-2.6) and phosphorus

2.08 mmol/l (N. 0.9-1.5). Arterial blood gas analysis showed a pH of 7.55, pCO_2 28.9 mmHg, bicarbonate 25.1 mmol/l, pO_2 95 mmHg and oxygen saturation of 97%. Fractional sodium excretion amounted to 0.7%.
Urinanalysis revealed mild haematuria (2-5 per field), leucocyturia (0-2 per field) but no casts, and mild proteinuria (0.8 g/l). Other biochemical and haematological laboratory values were normal or in the normal range. No measurements of myoglobin in serum or urine were performed. Additional testing for ANA, ENA, dsDNA, complement factor C3 and C4 levels and ANCA were negative or within the normal range. A chest radiograph and electrocardiogram were normal. Blood and urine cultures were negative. Serology *for Influenzavirus* types A and B, hepatitis B and C virus, Hantaanvirus, *Adenovirus, Mycoplasma pneumoniae, Chlamydia* spp, *Parainfluenzavirus* types 1, 2 and 3, *Toxoplasma gondii, Coxiella burnetii* and respiratory syncytial (Rs) virus was all negative. However, a fourfold rise in Coxsackie B2 antibody titre over a 14-day period was demonstrated (1:128 to 1:512), suggesting recent infection. The initial antibody titre was determined from a sample taken on the second day of hospitalisation (i.e., seven days after first onset of symptoms).
Despite immediate and vigorous hydration with normal saline and urine alkalisation with sodium bicarbonate to maintain a urine pH >7, the patient developed nonoliguric acute renal failure requiring temporary alternate-day haemodialysis three days after admission, which continued for two weeks (*figure 1*). Recovery was otherwise uneventful with a rapid decline in the serum creatine kinase (CK) level (*figure 1*), gradual disappearance of calf swelling and muscle pain, and almost complete recovery of renal function (creatinine on discharge from the hospital 150 µmol/l). At the time of his latest follow-up 18 months later, he had no further symptoms and the creatinine (108 µmol/l) remained stable.

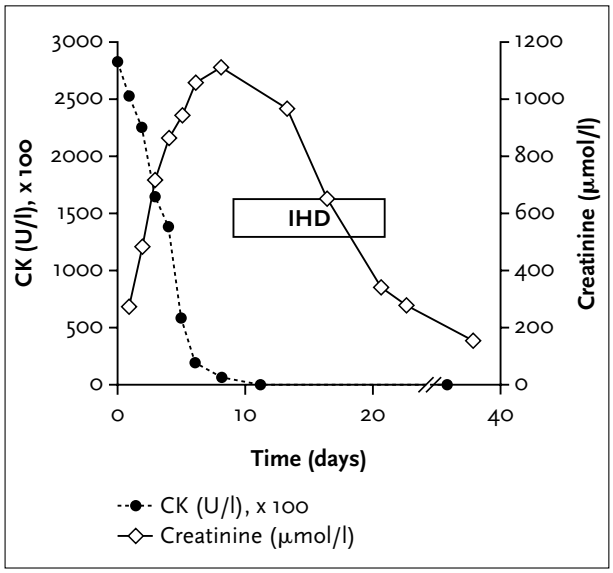

Figure 1
Time course of serum creatine phosphokinase (CK) and creatinine levels
Intermittent haemodialysis (IHD) was performed using a polysulphone hollow-fibre filter membrane (molecular cut-off point 20.0 kDa) with a blood flow rate of 200 ml/min and dialysate flow rate of 500 ml/min. Contrary to small molecules (e.g. creatinine, urea), large(r) molecules (>1.0 kDa) cannot be readily eliminated with diffusive techniques such as IHD.

DISCUSSION

We present a rare case of Coxsackie B virus-induced rhabdomyolysis, complicated by ARF. No symptoms of recurrent rhabdomyolysis were present, suggesting that an inherited disorder of muscle metabolism was highly improbable. In addition, other precipitating factors (e.g., alcohol, trauma, strenuous exercise or – less frequently – hypothyroidism, metabolic myopathies or drugs) were either absent or could be excluded in our patient.[5,6]
However, the onset of the disease as an upper respiratory tract infection with fever, headache and myalgia suggested a viral infection, which could be confirmed by a fourfold rise in Coxsackie B2 antibody titre over a 14-day period. Indeed, it is generally accepted that there should be a fourfold rise in antibody titre over a period of four to six weeks to make a definitive diagnosis of acute Coxsackievirus infection.[4]
Although considered rare, it is known that viral infections (notably *Influenzaviruses*) may induce a wide spectrum of muscle disorders, ranging from acute nonspecific myalgia to myositis.[6] To date, 11 cases of Coxsackievirus-induced rhabdomyolysis have been described in the literature, with a wide range of involved serotypes (A9, A16, B2-B6).[4-12] Their ages ranged from 9 to 57 (mean 30) years; male/female ratio was 0.6. Serum CK levels varied from 8500 to 685,000 U/l.[4-12] Although the precise mechanism of virus-induced rhabdomyolysis has still not been defined, it is assumed that initial acute tissue damage may be caused by the lytic effects of the virus on the muscle cell with subsequent release of myoglobin.[1,5,12] In experimental models, Coxsackie A9 and B5 injected into mouse resulted in muscle necrosis, suggesting that these viruses may indeed produce direct muscle damage.[4,5,12] The tropism of Coxsackieviruses for (striated) muscle is also illustrated by the isolation of this virus from the myocardium in patients with acute myocarditis.[1,2,5]
In three of the 11 reported cases, the course of disease was complicated by ARF necessitating intermittent haemodialysis for two to three weeks; all of them subsequently showing a complete recovery of renal function.[8,10] Our patient also

developed (nonoliguric) ARF despite vigorous hydration and urine alkalisation so that temporary intermittent haemodialysis was necessary for two weeks but subsequent recovery of renal function was also complete. ARF development caused by myoglobin may occur as a result of tubular obstruction by myoglobin, direct toxicity by haeme pigment, cortical ischaemia and decreased glomerular permeability resulting from fibrin strand deposition.[8,10] Dehydration, hypovolaemia and aciduria will accelerate this process. Of note, however, is that ARF has also been shown to occur as a result of an immune-complex mediated acute glomerulonephritis associated with recent Coxsackievirus B4 infection.[13]

It is suggested that, contrary to intermittent haemodialysis, use of convective dialysis techniques with large-pore membranes (i.e. haemofiltration) to remove myoglobin (MW 17.5 kDa) from the circulation may ameliorate or prevent impending ARF.[14] However, although substantial convective clearance of myoglobin can be found with haemofiltration (K_c 14-22 ml/min), myoglobin kinetics is such that endogeneous clearance is far superior to any form of therapeutic manipulation, even in the absence of renal function.[15]

In conclusion, a rare case of Coxsackie B virus-induced rhabdomyolysis and ARF in a previously healthy young man is described. Although most infections are asymptomatic, one should be aware of this potentially life-threatening complication of this virus. As illustrated with the present case, serological testing may reveal the diagnosis in a case of rhabdomyolysis after a viral illness.

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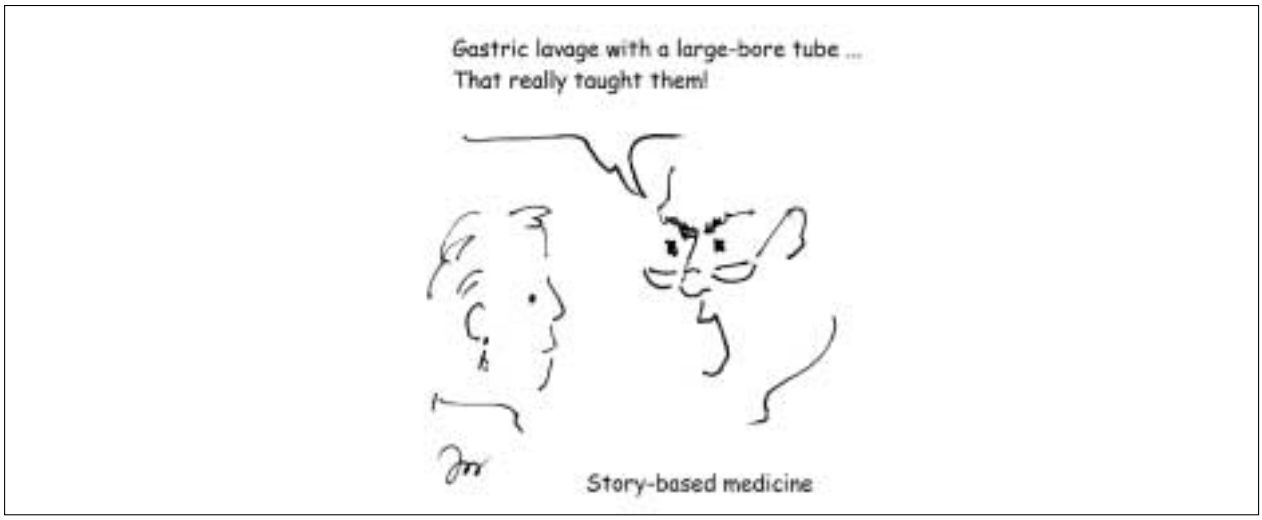

Fodili, et al. Severe rhabdomyolysis and acute renal failure following recent Coxsackie B virus infection.

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CASE REPORT

The woman who could not hold up her head

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ABSTRACT

Low serum potassium concentration is a frequently encountered abnormality, seldom accompanied by life-threatening symptoms. We present a 55-year-old women with a severe, symptomatic hypokalaemia. The pathogenesis and clinical manifestations are discussed.

INTRODUCTION

Hypokalaemia is perhaps the most common electrolyte abnormality encountered in clinical practice. It is found in over 20% of hospitalised patients.[1] Low concentrations may occur in up to 40% of outpatients treated with thiazide diuretics.[2] It is usually well tolerated. In extreme situations patients present with cardiac conduction abnormalities or paralysis. We present a patient with a life-threatening hypokalaemia.

CASE REPORT

A 55-year-old woman came to our emergency department complaining of difficulty in holding up her head. She had a history of Crohn's disease, for which she had undergone resections of the ileocoecum and neoterminal ileum in the past, and recently a further neoterminal ileum resection. She also suffered from chronic obstructive pulmonary disease (FEV_1: 1.29 l (57%)). She presented with severe weakness in her arms and legs, and stated that since the day before she had been unable to lift up her head. She also complained of shortness of breath and a nonproductive cough. She had no fever. Since her last operation she had had continuous diarrhoea; five to ten times a day with no obvious signs of blood. She had been on prednisone (25 mg a day) for three days because of shortness of breath. On examination we saw an ill-looking, dehydrated woman, with breathing difficulties. Her blood pressure was 175/95 mmHg, pulse 105 beats/min and temperature 36.7°C. Laboratory tests showed a Hb of 8.8 mmol/l (N. 7.5-9.9), WBC 18.6 x 10^6/l (N. 4-11 x 10^6), CRP 65 mg/l (N. <5), Na 148 mmol/l (N. 132-144), K 1.1 mmol/l (N. 3.6-4.8), creatinine 64 µmol/l (N. 62-106), Mg 0.29 mmol/l (N. 0.74-1.48), LDH 1020 U/l (N. 114-235) and CK 4170 U/l (N. 0-50). Urine analysis showed low excretion of magnesium and a normal potassium excretion. Arterial blood gas analysis revealed a pH 7.27, pO_2 10 kPa, pCO_2 9.7kPa, bicarbonate 32 mmol/l and an O_2 saturation of 90%. The electrocardiogram showed an abnormal atrial rhythm, normal QRS complex and peaked T waves with prominent U waves (*figure 1*). It was concluded that she was suffering from potassium and magnesium deficiency with muscle weakness, rhabdomyolysis, respiratory insufficiency and cardiac arrhythmia.

She was immediately transferred to the ICU for potassium and magnesium supplementation. Her potassium and magnesium levels normalised within 12 hours. With this treatment she recovered dramatically. The diarrhoea was treated and her electrolytes remained stable with oral supplementation. She was discharged from the hospital in a good clinical condition.

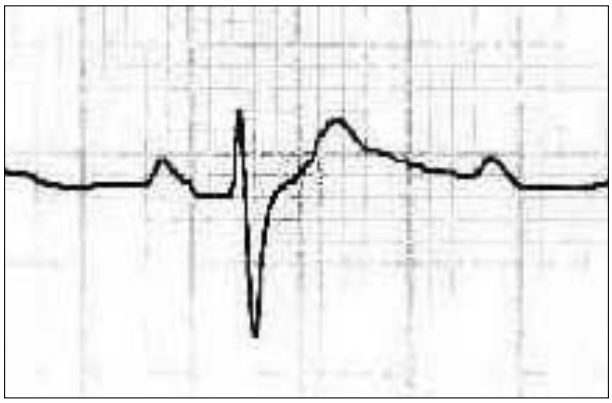

Figure 1
Registration of lead U_2: atrial rhythm, normal QRS complex with peaked T waves and prominent U waves

DISCUSSION

Patients with hypokalaemia often show no symptoms. When serum potassium levels drop below 3.0 mmol/l nonspecific symptoms may occur, such as muscle weakness. Also an increase in diastolic and systolic blood pressure can be seen. When the concentrations decrease below 2.5, rhabdomyolysis occurs and at concentrations below 2.0 an ascending paralysis can develop. Abnormalities in cardiac conduction can occur, especially in patients with an underlying cardiac disease. Typical electrocardiographic changes include flat T waves, ST-segment depression and prominent U waves. Causes of hypokalaemia can be divided into: 1) transcellular shifts due to insulin, catecholamines or B_2-adrenergic receptor stimulation, 2) low intake (<1 gram/day) and 3) abnormal stool or urinary loss, because of diuretic therapy, drugs with mineralocorticoid or glucocorticoid effects, use of laxatives or disorders accompanied by acid-base imbalances. Magnesium depletion, either due to low intake or abnormal loss, reduces the intracellular potassium concentration further and causes renal wasting.[2,3] In most cases low serum potassium concentration is secondary to drug treatment, particularly diuretics.
Our patient presented with a severe, symptomatic hypokalaemia and magnesium deficiency due to chronic diarrhoea after her last bowel resection. The hypernatraemia was due to the dehydration. She presented with muscle weakness, rhabdomyolysis, elevated blood pressure and cardiac conduction abnormalities. When we retrospectively analysed her laboratory results she already had a low serum potassium concentration (2.7 mmol/l) at discharge after her last operation. The acute lowering of the potassium concentration was probably due to the mineralocorticoid effect of prednisone.[2,4] Normally this leads to high urinary potassium loss. The reason why there was no high urinary potassium excretion probably lies in her longstanding and deep hypokalaemia. The acidosis was due to her extreme muscle weakness and therefore compromised respiration. Normally one would expect a higher bicarbonate level in a pure metabolically compensated respiratory acidosis but, probably due to faecal bicarbonate loss, this was not the case. So the acid-base disturbance in our patient was a combined one, due to respiratory and metabolic changes. The ECG abnormalities at presentation are in accordance with ECG changes seen in hypomagnesaemia (peaked T and U waves) and hypokalaemia (U waves).[5] After correction these abnormalities disappeared.
In patients with extreme muscle weakness and ECG abnormalities, the possibility of severe electrolyte abnormalities should be suspected and immediate correction is warranted.

ACKNOWLEDGMENTS

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ANSWER TO PHOTO QUIZ (ON PAGE 173)

OBLIVION AT THE KITCHEN TABLE

The cause of the skin lesions was not readily apparent to us. We suspected severe streptococcal disease and started penicillin and clindamycin.
Because of the metabolic acidosis and the urine analysis, we considered rhabdomyolysis with myoglobulinuria. Laboratory results revealed a creatinine kinase of 50,180 U/l and myoglobulin in urine was 126,800 µg/l. Rhabdomyolysis has been described as a complication of drug abuse.[1]
In the literature we found a report of seven patients with rhabdomyolysis who had similar eruptions due to prolonged positioning with pressure.[2] Pressure and hypoxia of tissue were considered important causative factors.
Our patient had been sitting at the kitchen table with his head resting on his right arm. All the cutaneous eruptions could be explained by pressure of the head on the right arm and vice versa, and of laced shoes on feet in dorsiflexion. Massive infusion of fluids and sodium bicarbonate prevented the need for haemodialysis. We stopped antibiotic therapy because of negative cultures of blood and blister fluids, and the eruptions healed. The patient made a full recovery.

DIAGNOSIS

We conclude that our patient was suffering from rhabdomyolysis due to drug abuse. The cutaneous eruptions were due to pressure because of prolonged positioning at the kitchen table.

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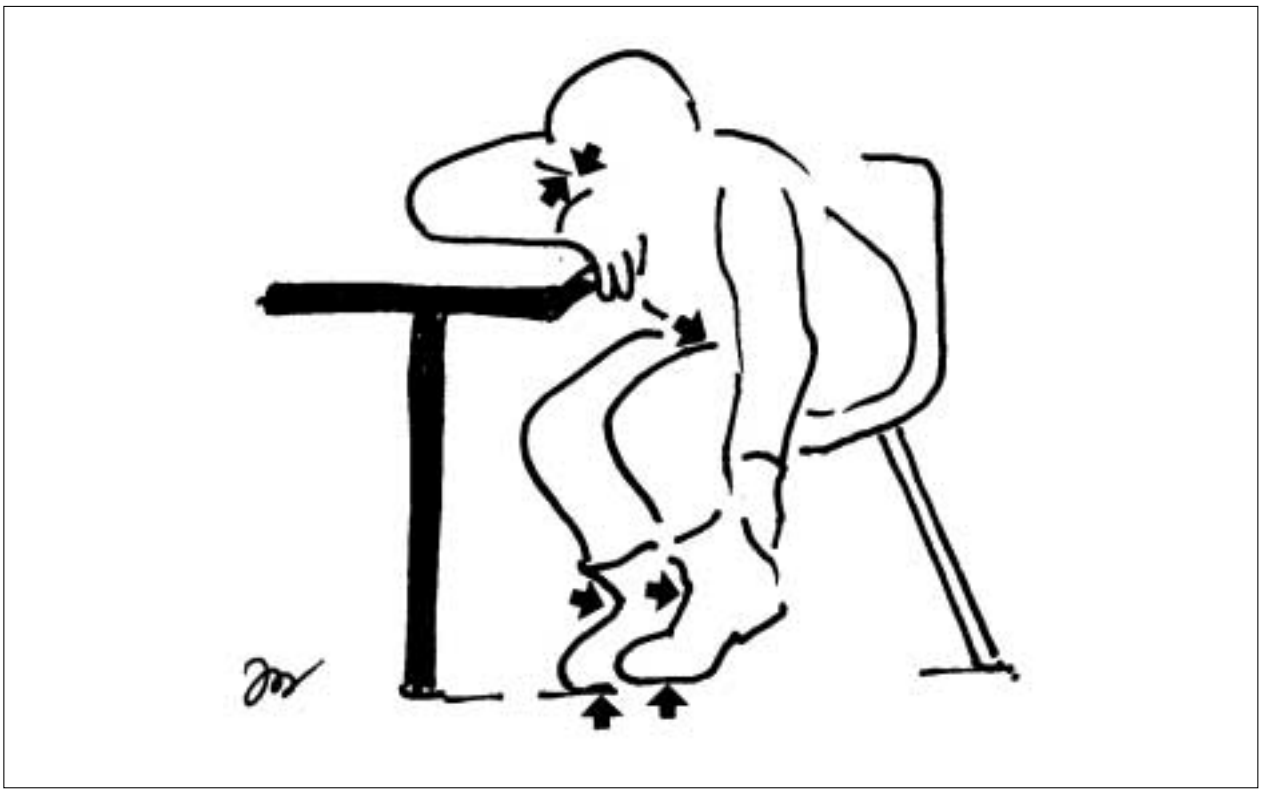
2. Miyamoto T, Ikehara A, Kobyashi T, Kitada S, Hagari Y, Mihara M. Cutaneous eruptions in coma patients with nontraumatic rhabdomyolysis. Dermatology 2001;203:233-7.



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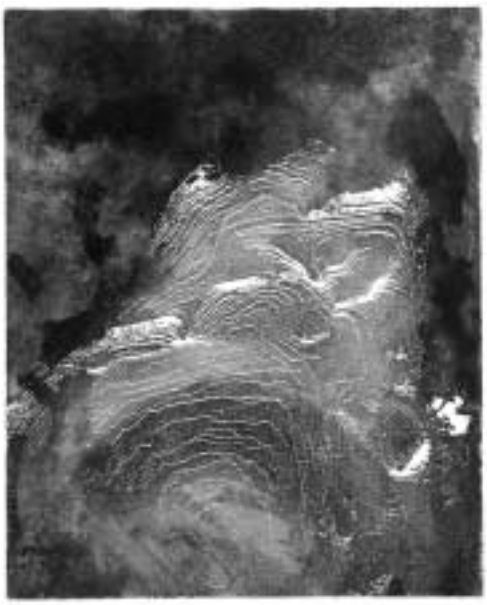
'Untitled'

Herma Deenen



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Examples:

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

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

[3.] Powell LW, Isselbacher KJ. Hemochromatosis. In: Harrison's Principles of Internal Medicine, 15th Edition, Braunwald E, Fauci AS, Kasper DL, et al. (eds). New York: McGraw-Hill; 2001. p. 2257-61.

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