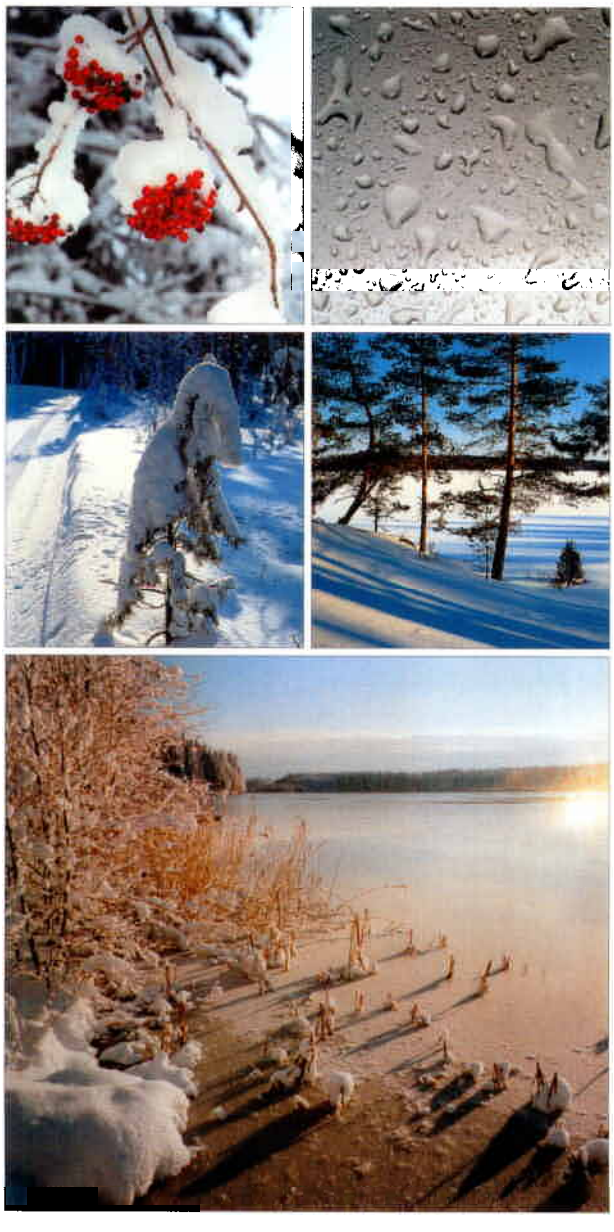
1.2000

TABU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA
LÄKEMEDELSINFORMATION FRÅN LÄKEMEDELSVERKET, FINLAND I DRUG INFORMATION FROM THE NATIONAL AGENCY FOR MEDICINES, FINLAND



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Summary

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Summary

Petri Pommelin
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National Agency for Medicines

Editorial

Quality control of medical devices

The National Agency for Medicines supervises that the medical devices on the Finnish market conform with regulations. We are part of EU's control system for medical devices, as provided under three directives concerning medical devices. The manufacturer is liable to prove the conformity with regulations of his product, and to that end, he shall affix the CE marking to each device as proof of conformity. As a rule, the manufacturer shall have a quality assurance system covering the design and manufacture of the product.

Another important function of the National Agency for Medicines is to promote the safe use of medical devices. With that objective, the Act on Medical Devices, in force since the beginning of 1995, includes regulations on the professional use of medical devices. Ensuring the safe functioning of medical devices, and the professional competence of the service staff, are some of the essential provisions under the Act. Furthermore, the providers of medical and health care services shall see to it that the users of medical devices have adequate training and experience, and that they have access to the necessary instructions for use. A record shall be kept of all medical devices either released for use or already in use; especially those implanted in patients. National Agency for Medicines shall be notified of any serious risk or hazard associated with the use of any such product.

These requirements lay the foundation for quality control aimed at ensuring safe use of medical devices. They have been included in the operational procedures of each centre for medical and health care services. The Government draft bill to amend the Act on Medical Devices, now being processed by the Parliament, contains further specifications and supplementary provisions.

In recent years, National Agency for Medicines has provided additional services on a commercial basis, for instance studies on specific hospital districts or health care districts, for use by local projects aiming at developing endoprosthetic surgery. In addition, National Agency for Medicines has issued a number of publications on the acquisition, use and maintenance of medical devices, with the intention of assisting medical and health care professionals in developing their own quality management procedures.

Last summer, the allergen-content of surgical and examination gloves made of natural rubber was investigated for the fourth time. The findings have been distributed to centres for medical and health care services. The National Agency for Medicines has also issued instructions on the sterilisation of medical devices and the hygienic practices applicable in dental care. Publications on hygienic practices applicable in dental laboratories, and on the acrylates used in dental care are being prepared.

Reports on the quality control of ultraviolet phototherapy and magnetic imaging were produced jointly with the Radiation and Nuclear Safety Authority. Together with the Medical Device Technology Branch of VTT Automation, the National Agency for Medicines has produced publications on the safety of medical electrical systems and on measuring the leakage current of medical electrical equipment. Guidelines for calibration of medical devices were published last autumn.

As the year 2000 began, centres for medical and health care services were put to practical test as to the success of the steps taken to eliminate the effect of the Y2K phenomenon in the medical devices. Contrary to the wildest prophecies, the New Year began peacefully. Major upsets were avoided, thanks to the careful preparatory work carried out at each centre, their key factors being well-functioning device registers and competent staff. In this regard, quality control was functioning acceptably. The next test will take place on the 29th of February in this leap year of 2000.

The National Agency for Medicines and the experts in this field are jointly geared to providing advice and instruction designed to promote the safe use of medical devices by the users and the service and personnel.

Översättning Mona Martin
Translation Liisa Fellman-Paul

Summary

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Parapharmaceutical products at the pharmacy

The prefix *para* is derived from the Greek and means beside, alongside, by the side of. Some European languages do recognize the concept, parapharmaceutical. It is used, for example, for products and services closely related to drugs or the business of pharmacies. This is also the meaning adopted in this article. Important topics of discussion in Finland in recent years have included, among others, the drug distribution monopoly held by the pharmacies, and the marketing and sales promotion procedures of pharmacies. In addition, various parapharmaceutical issues have also figured in the debate, such as the sale of homoeopathic, antroposophic or other similar products of natural medicines, which lack scientific evidence, but are similar to drugs, as well as the sale of cosmetic preparations or medical diagnostic devices and equipment. Measurements of blood pressure and blood glucose concentration are also included in this group. Many of these issues have been specified recently in detail by various orders of the authorities, but perhaps I may be allowed to discuss some of them from a purely philosophical point of view.

Is the retail sale of drugs the sole purpose of pharmacies?

Solutions to national problems in Finland are perhaps too eagerly sought from the EU nowadays. Even though the industrial production and marketing authorizations of drugs are, to a great extent, regulated centrally in the EU, answers to problems of development of the drug retail distribution system will not be found there. In fact, the opposite applies: a decision has been made within the EU whereby each country should resolve the situation independently as long as the citizens and businesses of all Member States are treated equally. Accordingly, Finland should recognize the academic degree of Master of Pharmacy gained in other EU countries as equivalent to the Finnish degree in questions of pharmacy licensing applications, for example.

The Nordic, very orthodox pharmacy system differs markedly from almost all drug distribution systems worldwide. Even though all consumer surveys have highly appraised the Finnish pharmacy system, demands have always been put forward for its change or "development towards a more international direction". In fact, the number of various cosmetic products for the treatment of skin and skin disorders has increased in the pharmacies in recent decades. This has probably avoided severe criticism since many preparations, which do not contain medicinal substances, are often even more recommendable than actual medicinal ointments. The opinion is more divided when the introduction of preparations of alternative medicine in the pharmacies is concerned. This group includes homoeopathic, antroposophic and many phytotherapeutic preparations. Pharmaceutical training units are advised to increase training in these areas. This has happened, in fact, but not in order for the pharmaceutical personnel to be able to recommend and sell products of alternative medicine, but in order for the pharmacists to know what the question is about when these subjects are discussed.

Evidence based medicine, i.e. orthodox medicine, is justifiably blamed in that it has neglected the human being in its admiration for high technology and top-notch research. The situation is being productively exploited by salesmen of alternative products. The following three facts should always be borne in mind by everybody – both those in favour of evidence based medicine and those in favour of alternative medicine:

1) the human being is a psychophysical entity,

2) the body heals many illnesses and complaints totally irrespective of treatment, and

3) in the end, we are faced with an illness incurable by any therapies.

In my view, the Finnish pharmacy system should always be based on research results supported by scientific proof. This view is also clearly shared by the medical authorities as well as by the professional pharmaceutical organizations. In no way should the pharmacies embark on the active marketing of therapies that lack scientific proof, however profitable it may be financially. Naturally, this will not exclude the possibility of the pharmacies to sell appropriately licensed alternative products among their own range of products to clients who wish to use them for some reason or other. In fact, it is a clear error of expertise to refuse to supply alternative medicine to a cancer patient requesting it in the terminal stage of illness by saying that the preparation is a load of nonsense. People must never be deprived of their hope to get better. But, they must not be robbed of their last pennies either; in fact, sellers of correct Lotto numbers have been prosecuted.

Ethical considerations become very important in discussions on

parapharmaceutical products. The true professional expertise of the pharmaceutical personnel is being judged in similar situations because detailed instructions on correct procedures are impossible to give. Consequently, the training of personnel in the pharmaceutical retail sector should be wide-ranging; it should have the correct theme and encourage independent decision-making.

Should pharmacies provide syringes and needles for drug abusers?

Should the pharmacy sell clean needles and syringes to abusers on intravenous drugs to prevent them from contracting an HIV or hepatitis infection through unclean equipment? This important topic cannot be merely answered by a yes or no. There are certainly situations where the only correct way of selling the requested products is selling them as effortlessly as possible. It should not be self-evident though that this is the procedure with all young and still healthy looking customers without even asking what the products are for. It may be important for a youngster in a changeable state to find that at least someone is interested in what he/she is going to do with his/her life. So far, the parents' care and responsibility for their child is found to be the only, even scientifically proven, factor protecting them against drug abuse. This is included in the conclusion of the consensus conference at Hanasaari on 3 November 1999, where treatment of drug dependency was discussed. Not even syringes should be sold automatically without question, because they are likely to be used for the dosing of chewing tobacco (snuff), which is the commonest cause of oral cancers.

Drug abuse is spreading in Finland like wild fire. Society should seriously concentrate on this problem. When the forest has been set ablaze, it is no use trying to put out the fire in single bushes without first having brought the entire forest fire under control. Like other illnesses, the most important and most efficient way to deal with this illness is probably prevention, which would primarily involve the frontier guard authorities, police authorities, and the judicial system. Naturally, treatment for those already suffering from drug abuse must be arranged. The consensus conference mentioned above found the most important form of treatment to be the so-called 'low-threshold therapy units', where acute personal problems, referral to long-term treatment and change of used syringes and needles to clean ones can all be dealt with as anonymously as possible. Contact with care personnel and the exchange of used needles and syringes for clean ones are particularly essential, and not only the sale of clean equipment. Change is also an important way to protect outsiders from the dangers caused by dirty needles. Consequently, the role of pharmacies is probably unlikely to become very important in the future when problems of drug abuse are being resolved.

The role of the pharmacy in the beginning of the 2000s

First pharmacies were specialized in the skilful preparation of drugs. However, drug preparation has gradually been removed from the pharmacies to drug manufacturers over the last hundred years. At the same time, drug research has introduced a large number of new drugs for us to use, which are considerably more effective than those used before – and, at the same time, more dangerous as well. Modern society needs pharmacies, not only for the retail distribution of drugs, but particularly because treatment with modern effective drugs requires an increasing degree of expert advice. The pharmacy has become part of the basic services in the health-care system.

The University of Helsinki has set its strategic aim for the beginning of this century to become a leading multidisciplinary university of the Baltic area. The Finnish pharmacy institution could form a leading drug retail distribution system, not only for the Baltic area, but also for the whole world. The business would be based on scientific evidence instead of erroneously using the marketing methods of alternative medicine, which often give the deceptive impression of being true. May the Finnish pharmacy of the 21st century be based on entrepreneurship and high-level professional expertise, and never ignore the rights and basic needs of the individual.

Summary

Irma Salovuori
GENERAL SECRETARY
The Board for Gene Technology
Ministry of Social Affairs and Health

Notifications of gene therapy tests

Legislation

There are two Council Directives that regulate the use of genetically modified organisms in the EU. One of them (90/219/EEC) deals with the contained use of genetically modified micro-organisms, and the other (90/220/EEC) with deliberate release of genetically modified organisms into the environment, i.e. research and development tests and the release of products on the market. The aim of the Directives is to ensure that the use of gene technology will not harm human health or the environment.

Our legal provisions differ from the EU Directives in that our law also provides for gene transfers in plants and animals. Section 1 of the Act provides that the legislation also covers the consideration of ethical viewpoints. To promote a general ethical review and discussion, the Act provides that the Board of Gene Technology should also include representatives of ethics and that a broad scale advisory committee is necessary.

Special legal provisions for genetically modified organisms, which are intended for use as foodstuffs, are found in the Regulation on novel foods and novel food ingredients.

The Gene Technology Act applies the use of genetically modified organisms. 'Organism' is defined as a biological structure that is able to produce or transfer genetic material. According to the legislation, organisms include also viruses and viroids, as well as cell and tissue cultures.

Revisions to legislation

Gene technology is a fast developing field of science and it requires revisions of legislation from time to time. The Council Directive on the contained use was recently revised. The amended Directive 81/98 was published in the Official Journal of the EC on 5 December 1998. The change will also have an effect on Finnish gene technology legislation, which will also be revised regarding these sections.

The review of the Directive on deliberate release is still underway and it may take up to a couple of years to complete. The review has included discussions on the application of the Directive on medicinal products. The discussions have concluded that medicinal products do not constitute part of the notification procedure of this Directive. This is supported by the fact that medicine is already well covered by its own legislation, including concern for environmental issues.

The supervisory and advisory role regarding compliance with the legal provisions of gene technology lies in health issues in particular, with the Ministry of Social Affairs and Health.

Expert authorities include the National Food Administration, the National Veterinary and Food Research Institute, the Plant Production Inspection Centre, the National Agency for Medicines and the Finnish Environment Agency. Expert institutions include the National Public Health Institute, the Agricultural Research Centre, the Forest Research Institute, the Institute of Occupational Health and the Technical Research Centre of Finland.

The Board for Gene Technology

The legally competent board is associated with the Ministry of Social Affairs and Health. The members of the Board represent various administrative sectors concerned with the use of gene technology: the Ministry of the Social Affairs and Health, the Environment, the Ministry of Trade and Industry and the Ministry of Agriculture and Forestry. Research and expertise in ethical issues are also represented by the members of the Board. The Board handles notifications according to the Gene Technology Act, provides instructions required in the application of the Act, acts as the registration authority and prepares statements to be issued to national and international authorities regarding the use of genetically modified organisms. The Board also supervises the use of genetically modified organisms and can restrict and prohibit the use of genetically modified organisms when necessary.

Notification procedure

Contained use includes tests carried out within gene therapy. Contained use covers all procedures and operations where organisms are genetically modified or where genetically modified organisms are cultured, stored, used, transported, destroyed, or

disposed of in conditions where physical, or in addition to physical also chemical or biological, methods of separation of organisms are used to prevent their potentially harmful contact with the public or the environment.

The Board should be notified of any tests carried out within gene therapy. Vectors used in gene therapy including virus vectors are genetically modified organisms referred to in the Gene Technology Act. When a vector is examined, developed, produced or used, notification of the premises where the work is carried out should be given to the Board according to the Gene Technology Decree. Appropriate notification must also be submitted for premises such as patients' quarters where genetically modified organisms are handled.

If genetically modified organisms can be considered harmless to humans and the environment a notification of premises is adequate. If it is considered that the genetically modified organism could be harmful to humans and the environment, then a separate notification of operations should be given according to the Decree. A separate notification is also required when the genetically modified organism or vector is not very well known. A new notification of procedures is also to be given when a new organism is introduced that does require a notification. The notification includes an assessment of the possible harm and a description of the procedures by which the risk is minimized.

What is required by the notification of premises and operations?

According to law, the notification of premises should include the following information where applicable:
1) the location of the unit and the name of the entrepreneur;
2) the names and qualifications of the persons responsible for the contained use of genetically modified micro-organisms;
3) genetically modified micro-organisms to be used, the level of safety of their use, their purpose, extent and control of use;
4) a description of the unit or the premises and the equipment important to the business;
5) a report on the measures of separation and safety referred to in Section 19 of the Decree;
6) waste management and other environmental protection measures required;
7) an emergency plan and a plan for the prevention of accidents; and
8) a summary of the assessment of any harmful effects expected on human health or the environment due to the planned use of genetically modified micro-organisms.

The notification of operations should include a more detailed description than the notification of premises of the actual procedure with particular emphasis on risk assessment and waste management.

Notification procedure

When a notification is received by the Board, its fulfilment of the legal requirements is ascertained. An expert opinion is requested when necessary. It is often necessary to request additional information from the entrepreneur. The Board for Gene Technology finally decides whether the business is allowed to start. The decision of the Board is communicated to the entrepreneur who may then embark on the project by taking into consideration any additional requirements proposed.

Conclusion

The Gene Technology Act regards only the possible risk to human health and the environment that may be caused by the genetically modified organisms outside human being in the tests carried out within gene therapy.

Applications for the approval of products of gene therapy are processed according to the medical legislation. The object of the therapy, a human being, is not covered by the Gene Technology Act. So far, three notifications of gene therapy have been received by the Board for Gene Technology.

The Gene Therapy Advisory Committee, set up in the UK in 1993, processes notifications of gene therapy and provides advice to users of gene therapy. Annual reports have been published by the Committee and can be found on its web page: **http://doh.gov.uk/genetics/gtac.htm**

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Inhaled glucocorticoids and the skin

Inhaled glucocorticoids have been used for the treatment of asthma since the 1970s. Their use is considered relatively safe, but in addition to their topical effect, they also have a systemic effect to some degree. Adverse dermatological effects of inhaled glucocorticoids, the majority of which are caused by reduced synthesis of collagen in the skin, have received little attention. Further information on their general occurrence has been obtained and the understanding of their mechanisms has improved during recent years. The biggest group at risk comprises elderly patients who, in addition to inhalation therapy, also receive oral steroid treatment. Any skin disorders caused by long-term treatment with inhaled glucocorticoids should be examined during follow-up visits, and the patient should be told about them when the treatment is introduced.

Glucocorticoids are known to affect the connective tissue of the body. They reduce the synthesis of several different types of collagen, e.g. types I, II, III and IV. A major part of the dry weight of skin is type I and type III collagen, and about 90% of the organic matrix of bone is type I collagen. Firstly, glucocorticoids influence the function of enzymes that break down collagen, i.e. collagenases, usually by reducing their activity. Secondly, glucocorticoids reduce the synthesis of another important structural part of the connective tissue, i.e. elastic fibrils or elastin. In addition to these effects, glucocorticoids regulate the activity of many other enzymes in the connective tissue, and they affect the metabolism of proteins.

UV radiation, including sunlight, has a significant effect on the connective tissue of the skin. Physiologically, female skin is thinner than male skin (about 0.8 x the thickness of male skin), and the skin becomes thinner by age. These factors should be considered in studies assessing the dermatological effects of glucocorticoids and the risk of glucocorticoids in clinical work.

Inhaled glucocorticoids and adverse effects on the skin

The undesirable effects of inhaled steroids can be topical, in which case it is a question of the adverse effects on the bronchi or oral mucosa. Systemic adverse effects are produced when glucocorticoids are absorbed mainly from the bronchi and the digestive tract.

The use of glucocorticoids increases the risk of bacterial, viral and fungal infections. Patients on glucocorticoid therapy are advised to rinse their mouth after taking the drug, primarily to prevent oral yeast infections, but also to reduce the absorption of the drug.

Soon after the launch of inhaled corticosteroids in the 1970s, bronchial biopsies showed epidermal atrophy or damage of collagen and elastin after 1–2 years of treatment. Maxwell and Webb reported on severe "easy bruising" in their patient who was administered 750 micrograms of beclomethasone twice daily in addition to other medication. Easy bruising is probably largely due to the reduced amount of connective tissue of the skin, especially collagen and elastin, which results in the skin becoming thinner and easily damaged; the veins of the skin become abnormally dilated, their wall becomes fragile and they are poorly supported against the surrounding tissue. The skin looks thin and translucent, the veins are clearly visible, and purpura and susceptibility to bruising can be seen. Striae caused by glucocorticoids, on the other hand, are due to reduced synthesis of the dermal elastin.

The prevalence of easy bruising in patients on inhaled glucocorticoids was compared with control patients in a questionnaire study by Mak et al. Patients receiving other drugs causing susceptibility to bruising such as anticoagulants were excluded from the study. 47% of patients on inhaled steroids (21.6% of control patients) had detected easy bruising, and the adverse effect was more pronounced in elderly patients and patients on large doses of steroids and long courses of treatment.

In-vitro and animal models have shown that systemic glucocorticoid inhibits the gene expression which controls the skin collagen synthesis by a concentration of 10-7 - 10-8 M. Such a concentration can be obtained from inhaled 400-microgram daily doses of budesonide. The metabolism of skin collagen is slow, however, and a short-term course of treatment with inhaled corticoids lasting for a few weeks is not long enough to produce adverse reactions.

Conclusion

According to sporadic reports, inhaled glucocorticoids can also cause allergy and acne. Adverse reactions of inhaled steroids on the skin are rare in children, but there is proof of growth and collagen synthesis disturbances. Further studies are required regarding the way in which the connective tissue of children's skin reacts to steroid treatment.

The risk of adverse effects is highest in the elderly as their treatment involves large doses, long courses of treatment and, in particular, if they receive treatment with corticosteroids also in forms other than inhalations. Consequently, it is recommended that the smallest possible doses be used in inhaled glucocorticoid therapy to minimize the adverse effects. Medical practitioners should be reminded of the importance of advising their patients of the possible adverse associated with the introduction of glucocorticoid inhalation therapy.

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Anaphylactic reaction caused by reteplase

The efficacy of thrombolytic treatment in myocardial infarction is inversely proportional to the delay of starting the treatment. In order to shorten delay, thrombolytic treatment is now more frequently begun outside the hospital, either in an outpatient care unit, in the ambulance or at the patient's home. Outpatient care doctors and ambulance personnel who are likely to become involved in thrombolytic treatment should be aware of the possible, albeit rare, occurrence of anaphylactic reactions. I will present a case of an anaphylactic reaction caused by reteplase which was managed admirably at an outpatient care unit.

The patient was a 54-year-old male who smoked and who had two years before been diagnosed with hypertension, hypercholesterolaemia and severe arteriosclerosis (ASO) in the lower limbs. The feeling of a heavy weight on his chest when cycling had caused him to slow down for one year before the hypertension was diagnosed. In connection with the diagnosis of hypertension, the patient's ECG showed clearly left ventricular hypertrophy and strain in the exercise test. Left ventricular hypertrophy was also detected on echocardiography, but systolic function was found to be normal. After introduction of antihypertensive treatment, only symptoms of ASO remained later exacerbating to a pregangrenous state. This made a femorofemoral bypass of the left limb necessary one year before the present illness. Allergy to penicillin was mentioned in the patient's records, but the nature of the allergic reaction was not further specified.

The patient developed chest pain one week previously and was admitted for treatment to a ward in the outpatient unit. No changes in the ECG or elevation of enzymes indicative of a myocardial lesion or infarction were found, and the patient returned home with no cardiac symptoms. Medication at home consisted of carvedilol 25 mg, enalapril 20 mg, isosorbide mononitrate 20 mg x 2, and acetylsalicylic acid 100 mg. Four days after discharge from hospital he suffered severe, tight chest pain at 9 a.m. and in addition to the medication prescribed for him to be taken at home, he also took chewable aspirin and isosorbide dinitrate in aerosol form, and sought emergency treatment at the outpatient unit.

On arrival at the outpatient care unit the patient was found to have stable haemodynamics: BP 180/100 mmHg, pulse rate 70/min, PO2 99%. At 10.24 a.m., marked ST segment elevation of up to 7 mm was noted in ECG V1-5 leads, indicative of anterior myocardial infarction, and thrombolytic treatment with reteplase was therefore started. Before the administration of reteplase an intravenous bolus of heparin was given according to instructions starting at 11.30 a.m., followed immediately thereafter by the first dose of reteplase, and followed by a second dose 10 minutes thereafter. A severe allergic reaction was triggered while the second injection of reteplase was being administered. The patient's lips and tongue swelled up, the blood pressure dropped until it became unmeasurable, but the patient remained conscious all the time. The treatment consisted of immediate administration of intramuscular adrenaline, intravenous Solu-Medrol 125 mg x 2 hourly, fluid therapy of Ringer's solution 1000 ml and Haemaccel 500 ml. An infusion of dopamine was started to enhance the positive inotropic effect. The pulse rate remained constant at 60-80, and no arrhythmias occurred. The blood pressure also recovered gradually to the level of 100/60 mmHg but required constant administration of dopamine (200 mg/100 ml) at the rate of 20 ml/hour. As the patient's condition became stable by 1.05 p.m. it was possible to transfer him to the Central Hospital.

On arrival at the Central Hospital the patient had no pain, BP was at 120/70 mmHg and pulse rate at 58, no clinical signs of congestive heart failure were detected, but the lower limbs were cool half way up, and the same applied to the arms. On ECG a QS complex was seen in leads V1-3, the ST segment was elevated only 2 mm, and a T inversion was present in leads V1-6.

Fluid replacement was continued by intravenous infusion of Ringer's solution 1000 ml, as a result of which his extremities warmed up, and the dopamine infusion could be discontinued. The rapid recovery from pain, with correction of ST segment elevation and early enzyme peak at six hours (CK 2116 and CK-MB 108 U/l) provided proof of successful thrombolytic treatment. Thereafter the patient recovered without haemodynamic problems. In an early stress exercise test, ischaemic changes were noted in the ECG by a small load (75W), and he was referred for coronary angiography. He was found to have a diffuse peripheral 3 vessel disease, good left ventricular function, and an ejection fraction of 69%. Consequently, conservative treatment was resumed.

Allergic reactions have often occurred in association with the administration of streptokinase. According to Pharmaca Fennica 1999, reteplase was recorded to have resulted only once in an anaphylactic reaction. GUSTO III study found an anaphylactic reaction in 0.05% of 100,138 patients treated with reteplase, and in 0.06% of 4,921 patients treated with alteplase. It is evident that our patient had successful thrombolysis irrespective of the allergic reaction, and effective initial treatment for the complication in the outpatient care unit led to a good end result. There was a risk of massive anterior wall myocardial infarction, but the final damage remained relatively small with also normal left ventricular systolic function. The patient had suffered chest pain prior to myocardial infarction which probably caused a preconditioning phenomenon in the heart muscle which protected the myocardium during the ischaemia, thereby diminishing the myocardial lesion. Reteplase is widely used because of its simple and rapid dosage effect. However, it is recommended that the personnel is prepared for any allergic reactions in spite of their rare occurrence.

Translation Mervi Moisander