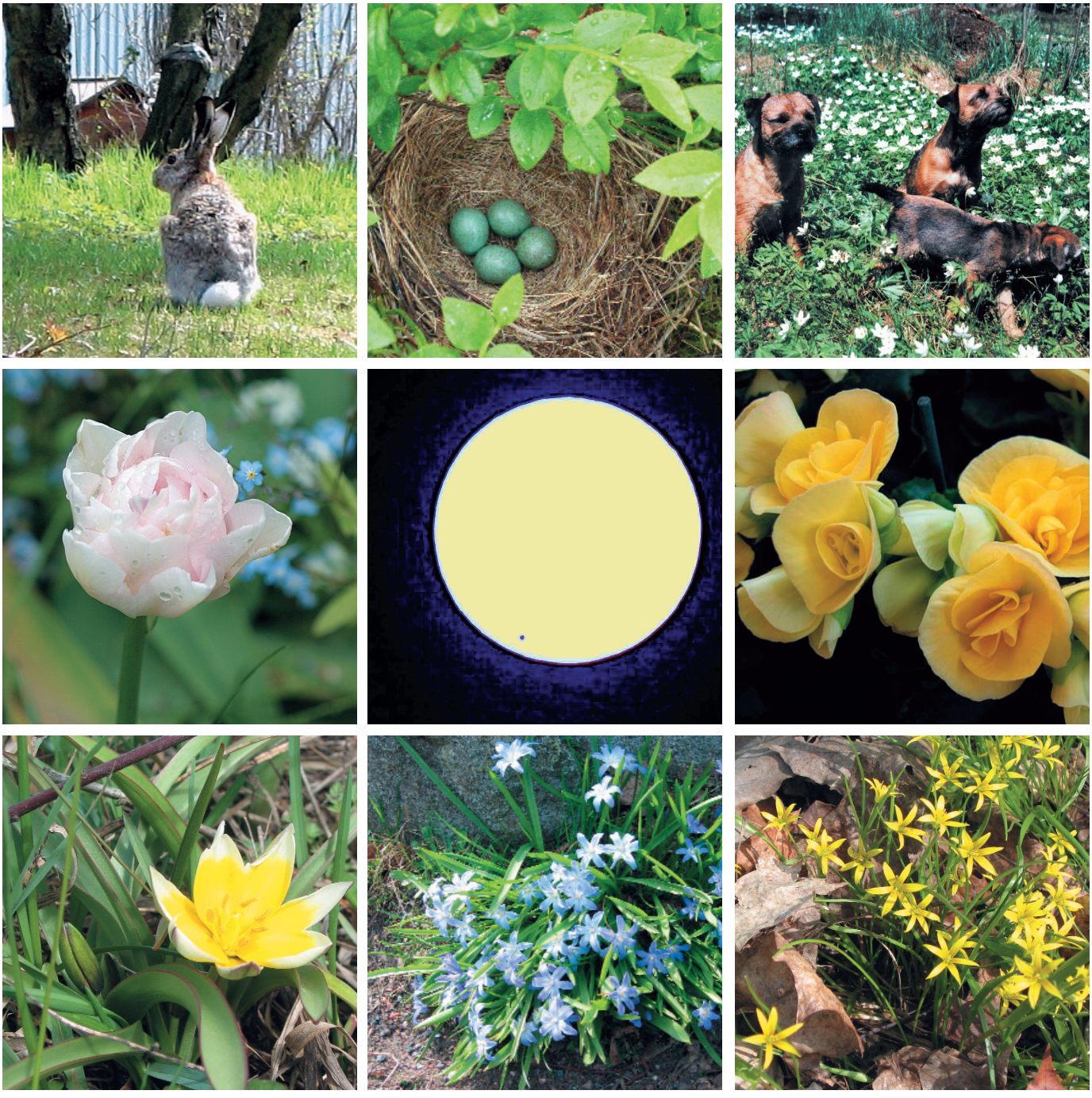
3.2004

TABU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA

LÄKEMEDELSINFORMATION FRÅN LÄKEMEDELSVERKET, FINLAND | DRUG INFORMATION FROM THE NATIONAL AGENCY FOR MEDICINES, FINLAND



3.2004

12. vuosikerta
12 årgången
12th Annual volume

Sammandrag

Summary

Summary

Hannes Wahlroos
Professor, Director General
National Agency for Medicines

Biological products and medicinal products for paediatric use

An important strategic decision was made by the National Agency for Medicines (NAM) in April with the aim of increasing its impact on EU issues. [1]

In co-operation with the EU, the NAM will in the coming years concentrate on issues in the sectors of biological products and medicinal products for paediatric use. In the biological products sector the emphasis lies especially on gene and cell therapy medicinal products and biotechnological products. The future strategy of the NAM in this changing and expanding area of medicines control within the EU can thereby be reinforced.

Efforts to centralise the regulatory work regarding new innovations will continue in the expanded union of 25 member states. Rational, high quality and resource-saving co-operation requires sensible sharing of duties and expertise among the authorities. It is also not credible that every agency, not even a large national institution, could be an expert in every area.

The NAM has great opportunities of success in the chosen areas of focus. The Agency has already developed expertise and know-how in the fields of biological products and medicinal products for paediatric use, and further development is to be expected. It is important that the front-rank Finnish expertise in these areas will be linked with the network of co-operation and experts of the Agency. The NAM wants to place itself in the forefront of the development of regulatory practices for advanced therapy medicinal products and their evaluation. The coming EU legislation covering medicinal products for paediatric use opens up new opportunities of influence.

With its areas of focus chosen the NAM nevertheless does not intend to neglect its future responsibilities in other areas of EU co-operation. The primary duties will be attended to without being hindered in any way. Notwithstanding this, the emphasis from now on will lie on, and important influential efforts will be concentrated on, the biological products and medicinal products for paediatric use.

The NAM is probably the first national medicines agency to reveal the strategy, which it has chosen for implementation in future co-operation within the regulatory work. It may well be that other drug authorities are making the same choices. In that case, we will have a case of co-operation and shared work opportunities, for which the chosen areas of focus, being as extensive as they are, will provide considerable opportunity. It would also be desirable for national centres of excellence to develop within the various areas of medicines control. In this way, sensibly shared duties would secure and promote public health of EU citizens in an ever more effective way.

We, at the National Agency for Medicines, would like to see that the choices made will be helpful to the research efforts in the pharmaceutical industry when the suitability of our Agency is considered for the responsibilities of evaluation, scientific advice and other expert assignments at the EU level. Biological products and the medical treatment of children are both extensive sectors under development and no doubt would be included in the research programmes of many pharmaceutical companies.

[1] See www.nam.fi, 6.4.2004

Olavi Tokola
Professor, Head of Department

Pekka Kurki
Head of Section

Markku Toivonen
Head of Section

Department of Marketing Authorisations

The National Agency for Medicines is focusing particular attention on medicinal product regulation in the EU

The targets of attention have been chosen by the National Agency for Medicines (NAM) and will be used to build up the strategy for the future and the conditions for credible and successful operation in the changing and developing field of activity. The enlargement of the EU will lead to the regulatory authorities of another 10 member states being able to share in the extensive area of responsibilities. It goes without saying that in order to achieve the best possible results the foundations of effective work by the European authorities must be laid not only on co-operation but also on specialisation.

Following discussions in the Agency, the areas of focus that have been chosen are biological medicines and paediatric drug therapy. Primarily, the choices will mean not only that the NAM will make a special contribution to EU co-operation especially in these areas of work, but will also naturally ensure that all of the authorities' duties will be carried out in an appropriate manner. The work will be systematically built up on the foundations of existing skills and competences.

Biological medicines

Biological products constitute a heterogeneous group. The conventional biological products include blood products, which have a key role in the healthcare system and which are partly covered by medicinal product regulation and partly by regulation of blood transfusion service operations. Vaccines are probably the most important medicines from the public health viewpoint. Most recent biotechnological medicines have been produced by using recombinant DNA or hybridoma technology. They have, for example, attained an important position in the treatment of diabetes and rheumatic and autoimmune diseases. Gene therapy and cell therapy are recent members in the group of biologicals; their most ambitious target is the recovery of tissue and organ functions lost due to congenital or aquired diseases.

Despite domestic setbacks in recent years, biological medicines are the fastest-growing group of medicine. About a third of the medicinal products being developed nowadays belong to this category. The authorities are faced with major challenges in the regulation of biological products. The development and regulation of new medicines is based not only on pharmacy and pharmacology, but also on cell and molecular biology, as well as immunology. Regulation makes use of the most recent scientific data, since the guidelines are not yet adequately developed or have to be finetuned on case by case basis. The choice and testing of raw materials and foolproof regulation of production methods are important means to ensure the safety of use of biological medicines, especially the safety of protecting against contamination with infective agents.

The regulation of biological products has always enjoyed a special status. Special legal requirements have been stipulated for blood products and vaccines, such as official product batch release. The centralised process for marketing authorisations for biotechnological medicines was adopted by the EU as early as 1987.

In recent years, by recruitment of experts and networking, the NAM has improved its expertise in the regulation of biological medicines. Experts of the NAM have participated in the scientific advise work, in the evaluation of marketing authorisations as rapporteurs and in the community referral processes dealing with biologicals. Experts from the Finnish Agency have often played a central role in the preparation of EU guidelines for biotechnological products.

The development of the biological products sector into a pivotal area started years ago. Nevertheless, the choice of biological products as one of the areas of focus in the process of exerting influence on the EU poses a considerable challenge. The quality and consistency of both scientific and administrative work in the special areas of focus need to be consilidated through continuous improvement of the skills required as well as trough increased interaction with academia. The small size of the Agency may be advantageous when trying to establish smooth collaboration of experts in biotechnology, pharmacy, toxicology and pharmacology in certain predetermined sectors of biotechnology.

Paediatric drug therapy

From the viewpoint of public health, paediatric drug therapy make up a very important but inadequately regarded field of pharmaceutical development. About 20% of the population within the EU area is under 16 years of age. These children and adolescents suffer from the same diseases as adults do, but in addition, they suffer from diseases absent in the adult population. The number of medicinal products authorised for marketing and intended for use in

children is restricted, since the pharmaceutical industry is producing new medicinal products primarily for use in adults. To a large extent, children are prescribed medicinal products on the basis of data collected from the experience gained in adults without appropriate trials and using pharmaceutical forms which are not designed for the needs of children. Should trials exist, they have not necessarily been submitted to the authorities for evaluation. Legal grounds for the EU authorities to demand such trials do not exist at present. Medicines for paediatric patients are typically developed in stages, and it may not necessarily be possible to launch trials concomitantly in different age groups, which may lead to a long delay.

The situation can be rectified only by legislative measures. The Commission issued a draft regulation on 8.3.2004 regarding medicinal products intended for paediatric use. Promotion of the status and health of children is the primary aim of the draft regulation. This is done by 1) promoting the development of new medicinal products and pharmaceutical forms for children, 2) ensuring that the medicinal products indicated for the treatment of children are based on a high level of research and authorisation processes, and 3) increasing and improving the information available about the effects of medicinal products on children. Support and incentives will be available for the pharmaceutical industry in its development work.

The key principle of the draft regulation is that every new applicant for a marketing authorisation for a new medicinal product must submit a paediatric development plan to the Board of Medicinal Products for Paediatric Use, which is to be established within the European Medicines Agency (EMEA), before the application for marketing authorisation is even considered for evaluation. The applicant may request a waiver from having to submit a paediatric development plan or request a postponement for the submission. A waiver can be granted under certain conditions. The aim is that the introduction of new important medicinal products indicated for adult use should not in any way be delayed. The draft regulation also stipulates that all paediatric trials associated with medicinal products which have a marketing authorisation in the EC must be submitted to the EMEA or to the national authority for evaluation within a year from the enforcement of the regulation. Once properly followed, these obligations are a significant challenge to the industry and the authorities. The aim of the draft regulation is also to ensure that the quality, efficacy and safety of old medicinal products, which have already lost the protection of their patent, are also investigated in cases where they are currently being used in children.

The NAM keeps a keen eye on the preparatory work associated with the regulation and is preparing itself to accept the associated challenges in pre- and post-authorisation control of medicinal products for paediatric use, both at the national and the EU level. This involves active participation in the work of the Board of Medicinal Products for Paediatric Use, which is to be established, by offering, for example, necessary expertise and accepting duties of evaluation respecting paediatric development plans and completed trials. Updating the data on medicinal products with national marketing authorisation is also an important aim. The Agency is already actively participating in the work of the paediatric expert group of the EMEA, the responsibilities of which include mapping out the problem areas in the medical treatment of children.

Scientific advice is available upon request regarding the conduct of tests and trials necessary to prove the quality, efficacy and safety of medicinal products indicated for use in children. The NAM has, for example, provided national advice and information relative to the development of pharmaceutical forms appropriate for use in children, and it takes an active part in the scientific advisory role of the EMEA by offering Finnish expertise and accepting responsibilities for co-ordinating the advice.

In-house training and support for the setting-up and maintenance of a network of experts are envisaged for enhancement of the expertise. The choice of biological medicinal products and medicinal products for paediatric use as the area of focus offers some advantages of synergy, because an ever-increasing number of the more recent medicinal products are classified as biological medicinal products. Many of the diseases treated with medicinal products based on gene and cell therapy appear already in childhood.

Conclusion

Biological medicinal products and medicinal products for paediatric use are important from the viewpoint of public health. To be able to exert influence in this area, the Agency needs good networks of cooperation and the continuous development of expertise and quality systems.

In May 2004, the EMEA carried out a survey among the national authorities on their strengths, potentials and targets of interest in the field of European medicinal product regulation. The decisions made by the Finnish Agency were timely and made it easier for Finland to complete the survey. The chosen areas of focus will gradually increase their share of the Agency's work involving its role as a rapporteur, its duties as a reference member state, its scientific advisory role, its choices of chairmen and the preparatory efforts of working groups, and its aims with respect to developing the skills of its staff, as well as in work involving post-authorisation control, pharmaco-vigilance and inspections.

Summary

Juha Tapanainen
PROFESSOR
Department of Obstetrics and Gynaecology
Oulu University Hospital

Male menopause

The male testosterone production is significantly reduced after middle age. Unlike menopause in women, the male climactericium, i.e. andropause is a continuous, slowly advancing process.

Decreased fertility is due mainly to slowly diminished sexual activity and not so much to changes in spermatogenesis. Sperm quality and motility are of course impaired, but the volume density of spermatozoa remains fairly constant. This is at least partly caused by the reduced frequency and volume of ejaculations. The concentration of free testosterone in the circulating blood is reduced by an average of one percent annually after the age of 40, leading to 30–40% lower concentrations in 70-year-olds compared with young men. The diurnal differences of testosterone secretion also even out with age. The reduction in free testosterone is associated with an increased amount of sex-hormone-binding globulin in the circulating blood. The exact cause of this is unknown, and neither is the reduction explained by the increased oestrogen to androgen ratio alone. Testosterone is changed to oestrogen and dihydrotestosterone (DHT), which is the most important active androgen in most tissues, including the prostate. The DHT concentration in the circulating blood remains fairly unchanged in elderly men. The production of androgen in the male adrenal gland is also beginning to fall after the age of 30, and in the over 70-year-olds it has dropped down to a third.

Why do androgens decrease?

The reduced number of Leydig cells, which produce androgens, and reduced blood circulation, causes the reduction in the testicular androgen production. The effect of the hypothalamus-secreted GnRH on the anterior pituitary and the tissue sensitivity to androgens are also reduced. Androgen deficiency classified as hypogonadism is found in less than 10% of men under the age of 60, but in at least 20% of the over 60-year-olds. There are significant individual variations and the testosterone concentration in some healthy men over the age of 80 is still equal to that of young adults. The reduced secretion and effect of androgen should distinctly increase the pituitary LH secretion. This is not always the case, however, and the LH levels in elderly men are often only slightly elevated or normal. This is an indication of reduced sensitivity of the hypothalamus-pituitary-testicle axis to hormonal feedback effects.

Andropause

The reduced hormonal function of the testicles and its associated changes are known as partial androgen deficiency of the ageing male (PADAM) or androgen decline in the ageing male (ADAM). Typical symptoms of andropause include reduced vitality, tiredness, irritability, depression, reduced sexual desire, sweating and hot flushes and also reduced muscle mass and strength. Memory impairment is also considered to be associated with reduced androgen levels. Many diseases, unhealthy life style such as smoking, high consumption of alcohol and lack of exercise encourage the reduction in androgen levels. Erection disturbances are common in ageing men. Less than a quarter of 40–45-year-old Finnish men suffer to some degree from erection disturbances, but they occur in nearly all 65–70-year-olds at least occasionally. Nevertheless, only about 15% of the cases can be explained by androgen deficiency.

Diagnostics and treatment of andropause

Androgen deficiency due to ageing is not always easy to detect, because most often it is a question of a relative deficiency, which causes symptoms of various degrees. Among clinical symptoms, night-time and morning erections correspond perhaps best to androgen concentrations. Erections occurring at a rate of less than one per week may be a sign of androgen deficiency. Lack of sexual desire may also indicate testosterone deficiency. Besides careful tracing of symptoms and clinical investigations, the initiation of androgen therapy should always be based on an assessment of the testosterone level. However, a serum testosterone level, which is low or even within the normal limits, does not necessarily reveal the whole truth. The weight and weight index of the male are ignored in testosterone reference values. If the total testosterone in an overweight male with apple type obesity is low, the free testosterone level may still be within normal limits because of high insulin concentrations and a low binding protein level. Similarly, a thin male may exhibit significant symptoms even at relatively high testosterone levels. If distinct symptoms of andropause are exhibited and the serum testosterone is below 10 nmol/l, androgen therapy is often beneficial to the male. At levels of 10–15 nmol/l, treatment for a trial period of 3–6 months may be considered and any alleviation of symptoms monitored.

Androgenproducts		*Dosage*
Oral products	*testosterone undecanoate capsules 40 mg* *mesterolone tablets 25 mg*	*120–160 mg/day* *25–75 mg/day*
Dermal preparations	*testosterone plaster 2,5 mg/24 h and 5 mg/24 h* *testosterone gel 50 mg/dose*	*2,5–5 mg/day* *dosepack/day*
Injection	*testosterone propionate/phenylpropionate/ -isocaproat/decanoat*	*250 mg in 3–4 weeks' intervall*
Depot injection	*testosterone undecanoat 1000 mg/dose*	*1000 mg in 3–4 months' intervall*

Testosterone products

Testosterone treatment may be administered orally, by intramuscular injection, or cutaneously in plasters and gel products. Testosterone levels achieved by an oral testosterone derivative vary considerably, depending on the absorption and liver breakdown of the medicinal substance. Because of the rapid breakdown, the product should be taken three times a day to obtain a balanced hormonal effect. The most common product is testosterone undecenoate, which is administered at a dose of 80 mg in the morning and 40 mg during the day and in the evening. Some men may require a daily dose of as high as 240 mg. By using this method of administration, excessive increases in the testosterone level are avoided.

A testosterone injection (200–250 mg) is administered at intervals of 3–4 weeks. Steady concentrations are achieved by daily testosterone plasters, or gels, or depot injection which will be administrated im. in 3-4 months' intervall.

The efficacy of hormone treatment is assessed at a doctor's appointment after 3–6 months. Measurements of serum testosterone levels are usually of no benefit because of the reduced secretion of endogenous testosterone and other androgens, and a radioimmunological assay is not helpful in the assessment of bioactive androgen levels. Subjective clinical responses are therefore the most important parameter of response.

Adverse reactions

Androgens used in replacement therapy have relatively few adverse effects. Greasy skin, acne, breast tenderness/enlargement and oedema in the limbs may be signs of an excessive dose. The lipid effects of androgen are dependent on the product and the dose, but physiological treatment has an insignificant effect on the fat values. Liver function disorders are rare during treatment. They may occur in the use of methylated testosterone products, but products devoid of methyl testosterone content are usually safe to use. It is recommended that cholesterol and liver enzyme levels be checked at the start of treatment. Androgens accelerate erythropoiesis, and consequently, the haemoglobin and haematocrit levels should be assessed annually and the dose reduced as necessary. This is usually not a problem if the initial levels of testosterone are distinctly low. On the other hand, in the treatment of a relative androgen deficiency, the haemoglobin and haematocrit levels may increase significantly. Long-term androgen therapy may delay spermatogenesis due to reduced secretion of gonadotrophin, but according to available data the changes are reversible.

Prostate cancer must be excluded prior to the start of the treatment. Palpation of the prostate via the anus and evaluation of the serum prostate specific antigen (PSA) are usually sufficient. Androgen therapy has not been found to increase the occurrence of prostate cancer, but it may promote the advancement of existing cancer. As the follow-up times of androgen treatment are still relatively short, the prostate and PSA should be examined every year. For the same reason, the treatment should be withdrawn if it is of no definite benefit to the patient. No definitive adverse effects on benign prostatic hyperplasia have been detected with androgen replacement therapy. The occurrence of sleep apnoea may increase during testosterone therapy. The blood oestradiol concentration is increased by testosterone therapy, which results in a relatively frequent occurrence of gynaecomastia in elderly males.

Conclusion

Ageing is accompanied by a number of symptoms and complaints, some of which are associated with andropause. The most important symptoms distinctly associated with the reduction in androgen levels include changes relating to general wellbeing and libido. Since nearly all changes, both physiological and pathological, linked with ageing, are caused by several factors, it is often difficult to decide whether the symptoms exhibited are a result of reduced testosterone levels and whether androgen replacement therapy would be of use. Initiation of the treatment should be based on both past medical history and evaluation of the testosterone level. The efficacy and necessity of androgen therapy can be established with a couple of months' trial therapy. If a distinct response is not achieved within half a year, treatment with the same product is not recommended, because the risks of long-term therapy are not very well known. It should be borne in mind that only some males require testosterone therapy and find it beneficial. A large proportion of males becomes grey and old happily without recognising any androgen deficiency. Let's not get involved in unnecessary examinations and therapies without distinct symptoms and findings indicative of a hormone deficiency.

Summary

Jyrki Vanakoski
Senior medical Officer

Leena Sommarberg
Researcher

Safety&Drug Information
National Agency for Medicines

Adverse drug reactions involving the skin and subcutaneous tissue reported to the National Agency for Medicines during 1973–2003

Various skin reactions are thought to be the most common ADRs, but for a number of reasons it is difficult to obtain a definite picture of exactly how common they are. Drug reactions, by the symptoms they exhibit, do not normally differ from skin reactions arising from other causes. Furthermore, undefined skin reactions, and particularly reactions with mild symptoms may easily go unreported.

In relation to drug consumption, the proportion of skin reactions caused by medicinal substances is estimated at 2%. Indications of the prevalence of skin reactions in relation to other adverse drug reactions are probably to be seen in the fact that 5,862, or 30% of all reports received by the Agency in 1973–2003, were associated with suspected reactions in the skin or subcutaneous tissue.

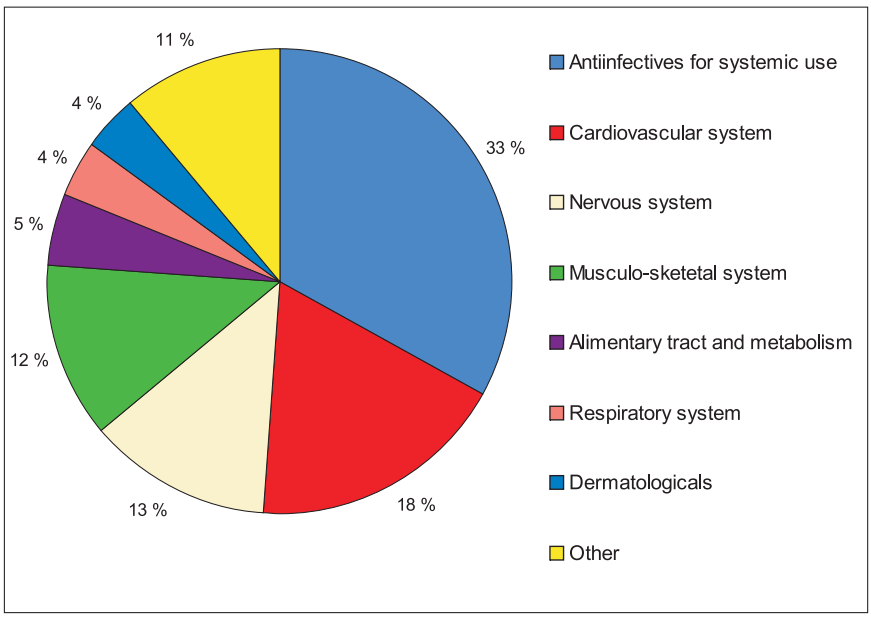
In the various drug groups adverse skin reactions were most commonly reported with the use of antiinfectives for systemic use, drugs for cardiovascular diseases, and drugs having an effect on the nervous system (Fig.). The five most commonly reported categories of ADRs covered almost 75% of all adverse reactions of the skin and subcutaneous tissue, three of them being urticaria (24% of all reports), more general "rash" (22%) and erythematous rash (17%).

Angioedema

A total of 124 cases of angioedema (2% of all reports), manifested as oedema of the subcutaneous tissue and mucous membranes, was reported during 1973–2003. The highest number of reports were of drugs used in cardiovascular diseases, and in almost half of the cases of angioedema, i.e. 49 reports, the suspected medicinal substancies were ACE inhibitors, while 11 reports were concerned with a combination of an ACE inhibitor and a thiazide diuretic. A total of 34 reports on ACE inhibitors were associated with enalapril. The next most commonly reported cases of angioedema were associated with the use of losartan and a combination of losartan and a thiazide diuretic (7 reports) and the use of acetylsalicylic acid (4 reports).

Erythema fixum

Erythema fixum is almost without exception regarded as a skin reaction caused only by medicinal substances. On recurrence it always reappears in the same skin areas. The ADR database of the NAM contains 100 reports of erythema



fixum over the past 30 years. The most commonly reported reactions were manifested during the use of doxycycline (15 reports) and sulphonamide and trimethoprim and their fixed combinations (12 reports). In the 1970s and 1980s, fixed analgesic combinations containing phenazone, which have since been withdrawn from the market, were the most common group of products (12 reports) associated with erythema fixum reactions.

Photosensitivity reactions

Medicinal substances known for the photosensitivity reactions they cause include doxycycline, fluoroquinolones, chlorpromazine among neuroleptics, and some topically applied anti-inflammatory analgesics. The 95 cases of photosensitivity reported are fairly evenly distributed over the various active agents or their combinations. The most commonly reported products were a combination of amiloride and hydrochlorthiazide (9 reports), and doxycycline (7 reports). Six reports of adverse drug reactions were associated with the use of sulphonamides and combinations of them with trimethoprim, and with the use of anti-inflammatory analgesics such as piroxicam and ketoprofen; the reports of the latter were, all but one, associated with a pharmaceutical form intended for topical use.

Serious skin reactions

Erythema multiforme and the more serious Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) are nowadays classified as different forms of the same syndrome. In addition to blisters on the skin, Stevens-Johnson syndrome is associated with blisters on the mucous membranes and general symptoms, e.g. fever. Due to the necrosis of extensive areas of skin associated with toxic epidermal necrolysis, and due to the damage to the mucous membranes, intensive care is indicated, and the state is often life-threatening. The number of reactions suspected to have been associated with drug exposure during 1973–2003 was 291, i.e. 5% of all skin reactions. A total of 152 reports were associated with erythema multiforme, 105 with Stevens-Johnson syndrome and 34 with toxic epidermal necrolysis. Over half of the reported cases of Stevens-Johnson syndrome and all of those of toxic epidermal necrolysis were classified as serious adverse reactions. In addition, six of the cases of toxic epidermal necrolysis caused a patient's death. Of all the reports, 73 reactions were suspected of having been caused by sulphonamides, trimethoprim or their combination. Other most commonly reported individual medicinal substances included terbinafine (19 reports), carbamazepine (17 reports) and sulphasalazine and phenytoin (9 reports of each). In the reports associated with toxic epidermal necrolysis, the most commonly suspected medicinal substances after sulphonamides and trimethoprim were carbamazepine and phenytoin.

Conclusion

Reactions of the skin and subcutaneous tissues are some of the most commonly reported ADRs. The majority of them are nevertheless mild, and withdrawal of the medicinal substance and its subsequent avoidance as far as possible are usually adequate as treatment. At the same time, however, it needs to be borne in mind that a small proportion of the skin and mucous membrane reactions may be life-threatening, and that they may be induced by the same commonly used medicinal substances as those which have been in use when a mild reaction has occurred.

Literature

Alanko K. Lääkeihottumat. Kirjassa Hannuksela M, Karvonen J, Reunala T, Suhonen R (toim.) Ihotaudit, ss. 142-150, Kustannus Oy Duodecim, 2003.

Felix RH, Smith AG. Skin disorders. In book Davies DM (ed.) Textbook of adverse drug reactions, pp. 514-534, Oxford University Press, 1991.

Himberg J-J, Kuitunen T. Lääkkeiden haittavaikutukset. Kirjassa Neuvonen PJ, Himberg J-J, Huupponen R, Kivistö KT, Ylitalo P. (toim.) Kliininen farmakologia ja lääkehoito, ss. 813-814, Kandidaattikustannus Oy, 2002.

Translation Mervi Moisander