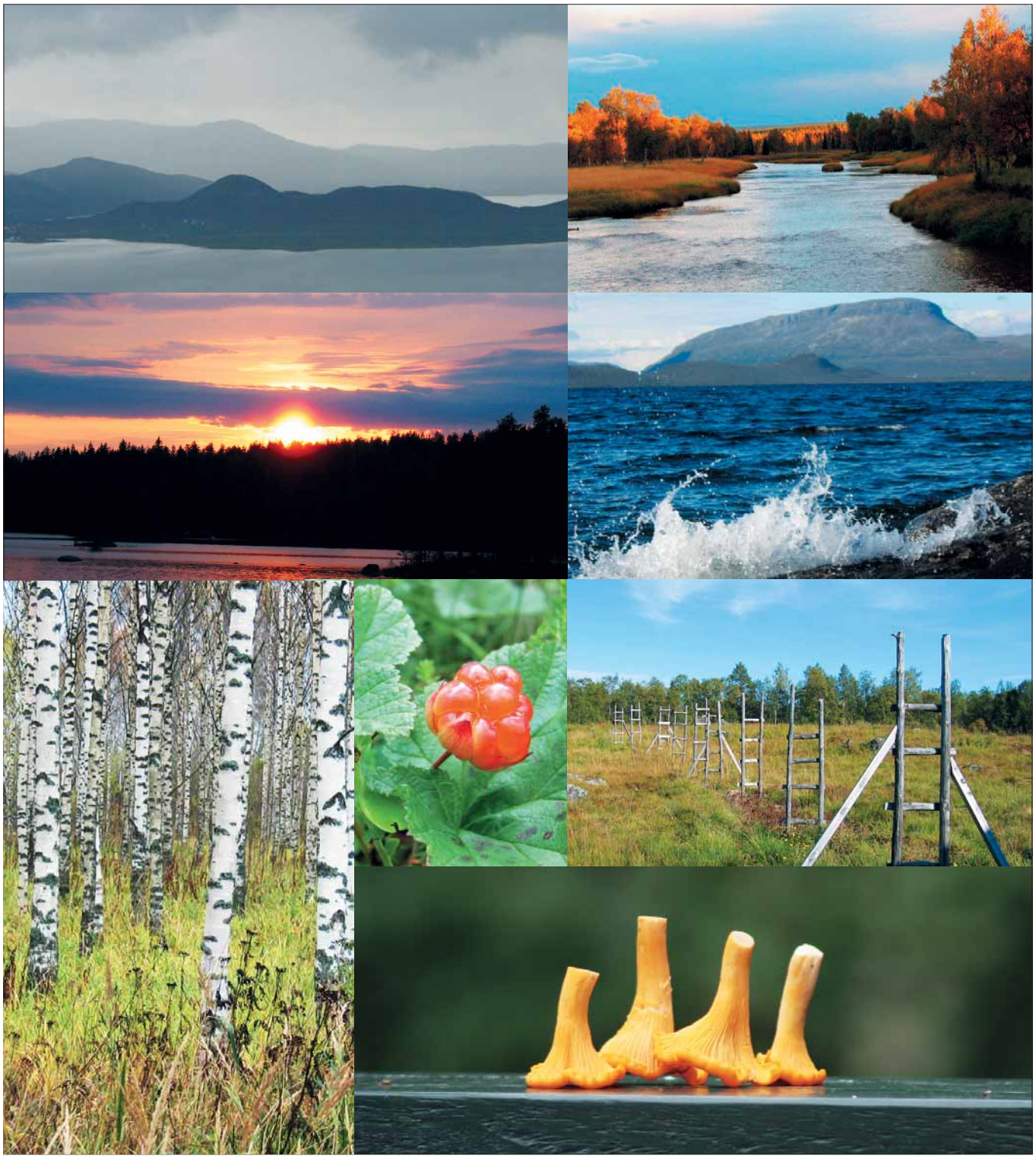
TABU

Lääkeinformaatiota Lääkelaitokselta

Läkemedelsinformation från
Läkemedelsverket, Finland

Drug information from the National
Agency for Medicines, Finland

5|2005



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Editorial

New technology increases the need for supervision

The European Commission is preparing legislation with regard to advanced therapies created by new technology.[1] The legislation deals with gene therapy, cell therapy, tissue engineering and other new technologies which support these. The draft proposal of the Commission concerning the supervision of products and the associated marketing authorisation procedures has been made available for comments from all interested parties.

It is reckoned that the products of new technology will have a significant impact on health care, and the products have several scientific, economic and ethical aspects in common. The products are based on complicated, high-tech manufacturing processes, the scientific and supervisory expertise in the product area is scarce, and protection against infection is one of the key issues of safety. These products are often developed by small and medium-sized biotechnology firms.

The new advanced therapies are expected to be of significant benefit in, for example, the treatment of cancer, as well as the treatment of Alzheimer's and Parkinson's diseases. Regenerative medicine, by which disease paths are changed and which may in the end make it possible to grow tissues topically in the human body, is also a current focus of attention. The new therapies are presumably more costly than conventional drug therapies. In view of the tight monetary framework of health care this aspect will also no doubt make prioritisation and more rational drug treatment necessary.

The aim of the new supervisory measures is to ensure a high level of safety for patients. The prerequisites for product introductions on to the market, and the supervision of the safety of products already available on the market, will be harmonised. The aim is also to improve the preconditions of competition among companies operating in Europe and to ensure flexibility at a level of regulation adequate for scientific and technological development.

Safety is also being improved in other ways. A Directive on human tissue[2] was approved in March 2004, the aim of which is to ensure the quality and safety of human tissues and cells to be used in humans. The Directive will be enforced nationally by 7.4.2006. The Directive deals, for example, with the supervision of procurement of human tissues and cells, as well as the accreditation, licenses and inspections of tissue institutions. The stem cells of adults and embryos also fall within the scope of application of the Directive. It is proposed that the National Agency for Medicines takes on the role of a supervisory authority in respect of 'tissue institutions', i.e. tissue banks.

New therapeutic alternatives are associated with known and also unexpected risks. The best known ones probably include microbiological contamination of source materials and production processes, including the spread of diseases, natural variation in the source materials, incompatibility of bio-materials and tumorogenicity of products. The National Agency for Medicines in Finland has submitted a review to the Ministry of Social Affairs and Health on the 'safety of products containing material of human origin'.

The requirements and measures of modern pharmaceutical supervision have developed during the past 40 years. The intention is, in fact, to make use of the experience gained thereby in the supervision of tissue engineering products. It appears that the European Medicines Agency (EMEA) will assume a new duty role in the scientific evaluation of tissue engineering products. This would have a natural reflection in the requirements for expertise of the competent authorities for pharmaceuticals in each Member State, as all these authorities already work in close collaboration with the EMEA.

The development of products containing material of human origin is a growing sector of technology. Products are already available commercially worldwide. Scientific and technological development will not, however, wait for legislative developments, and supervision would also require new ways of thinking. It would be in the best interest of the patients, the development of the sector, and the industry, if the supervisory arrangements were created at an early stage. This would dispel the uncertainties associated with safety requirements, promote the development and competitiveness of companies and expedite the introduction of the new products into health and patient care.

[1] *http://pharmacos.eudra.org/F2/advtherapies/index.htm*
[2] *Official Journal of the European Union L102, 7.4.2004, p. 48*

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Recommendations for the medical therapy of the elderly

Expert recommendations for medical care of the elderly have been issued in many countries, especially with regard to the drugs which are to be avoided. The recommendations issued in Sweden in 2003 emphasise the avoidance, for example, of long-acting benzodiazepines, i.e. diazepam, chlordiazepoxide and nitrazepam, potent anticholinergics, oral theophylline, and quinine, because of the associated risk of adverse reactions.

Changes in the human body associated with ageing also change the absorption, distribution, degradation and elimination of drugs. The proportion of water of the total body weight is decreasing and the proportion of fat is increasing. The distribution volume of fat-soluble medicinal substances is increasing and their elimination is decreasing. The distribution volume of water-soluble medicinal substances is decreasing. The hepatic circulation is reduced, and the function of some drug catalysing enzymes is also reduced. The capacity of the kidneys to secrete medicinal substances and the products of their degradation is reduced and is at the age of 75–80 about half of the secretion capacity of a young adult (1). Creatinine production is reduced as the muscle mass is decreasing, and the serum creatinine concentration therefore poorly reflects the renal function of the elderly. Creatinine clearance and serum cystatine C concentration are superior methods of assaying this (2).

The sensitivity of tissues and cells to drug effects is increased, and the capacity to tolerate the harmful side-effects of drugs is reduced. The elderly are especially predisposed to the brain function reducing adverse effects of benzodiazepines, opioids, anticholinergic agents and antipsychotic drugs, such as impairment of the memory and other cognitive abilities, and confusion. Reduced baroreceptor reflex predisposes them to the development of ortostatic hypotension, for example when vasodilators, diuretics, anti-Parkinson drugs, antipsychotics or tricyclic antidepressants are used (1).

Attempts to solve the problems associated with medical treatment of the elderly have been made in many countries by arranging further training for doctors and other health care employees and by employing experts in clinical pharmacy at care institutions (3). The experts have issued guidelines for the clinical use and general evaluation of medical treatment (4, 5, 6, 7). Furthermore, in the USA, the use of antipsychotics in long-term care institutions has been restricted. The monitoring of practices in the medical treatment at care institutions shows that, in long-term care institutions, the use of drugs under regulatory restrictions is relatively rare (8, 9, 10).

In this paper we discuss the general recommendations for medical treatment of the elderly issued by a Swedish group of experts (7). We also discuss some of the general problems associated with medical treatment of the elderly in Finland, and suggest measures which we consider necessary.

Expert recommendations

The expert recommendations issued in Sweden stipulate which medicines should be avoided in the treatment of the elderly, the length of time for which certain medicines may be given, the ways in which the effects and adverse reactions of the substances should be monitored, and which substance combinations to avoid. These guidelines are thus concerned with medicinal substances and do not constitute instructions for the treatment of diseases. In addition to the general guidelines, recommendations for drug therapies in some diseases are also given. The general recommendations, which are not specific to any particular disease, are based on international recommendations and differ scarcely at all from the guidelines given in other countries (7).

Medicines to be avoided without a special consideration

Medicines with a long half-life, such as benzodiazepine derivatives i.e. diazepam, chlordiazepoxide and nitrazepam, highly anticholinergic agents, oral theophylline and quinine are agents which should be avoided in the treatment of the elderly (7).

Fat-soluble medicinal substances have a longer half-life in the elderly than in the middle-aged population. Benzodiazepine derivatives, which already have a long half-life as it is, have a very long half-life in the elderly, and the associated risk of accumulation is high. Tiredness, impairment of memory and other cognitive abilities, confusion, muscle weakness, co-ordination problems and falling down are generally reported adverse reactions (7).

Impairment of memory and other cognitive abilities, confusion and behavioural disorders, in addition to constipation, dryness of the mouth and visual disturbances, are adverse reactions in the elderly generally

caused by potent anticholinergic agents. The efficacy of anticholinergic agents for the treatment of urinary incontinence has not been proven in the treatment of urinary incontinence in the elderly. These are grounds for avoiding the use of the above mentioned agents (7).

Theophylline has a narrow therapeutic range, adverse effects and interactions with several medicines. Proof of its effect in the treatment of adult onset asthma and of chronic obstructive pulmonary disease is inadequate. Oral theophylline should therefore be avoided.

The adverse reactions of quinine include confusion and thrombocytopenia. It is consequently considered a drug to be avoided in the treatment of the elderly (7).

Medicines for which correct indications are necessary

The following section contains medicinal substances which are problematic as to their adverse effects and interactions and which, as studies show, are prescribed to the elderly relatively commonly without indications to justify their use. The necessity for critical assessment in the prescription of anti-inflammatory drugs, opioids, antipsychotics, digoxin, loop diuretics and serotonin-selective antidepressants is emphasised. (7).

Gastrointestinal ulcers and haemorrhages, fluid retention, cardiac insufficiency, reduced renal function and cognitive disturbances are adverse reactions caused by anti-inflammatory analgesics in the elderly. Paracetamol is a relatively safe medicinal substance for the treatment of pain in the musculoskeletal system in the elderly. Anti-inflammatory analgesics should not be used unless their use is associated with benefits greater than those with paracetamol (7).

An opioid, e.g. codeine or tramadol, may erroneously be prescribed for long-term use without evaluation of the effects of the treatment. The use of opioids should always be based on a specific diagnosis of the cause of the pain, and the effects of the treatment and adverse reactions should be monitored. Tiredness, adverse cognitive effects, confusion and falling down are the adverse reactions of these drugs exhibited in the elderly. The benefits of the treatment must be bigger than the adverse effects (7).

Codeine and tramadol are prodrugs, which may be ineffective as a result of the use of another medicine or a genetic property. They are activated by the effect of enzyme cytochrome P450 2D6. Fluoxetine, quinidine, parecoxib and terbinafine are potent inhibitors of this effect. They, including celecoxib, several antipsychotic drugs (e.g. haloperidol, risperidone and phenothiazine derivatives), paroxetine and amitriptyline impair the analgesic effect of tramadol and codeine (11). These drugs should not be used concomitantly with codeine or tramadol.

Tramadol is serotonergic and its use concomitantly with an antidepressant may cause a serotonin syndrome. Tramadol should not be prescribed if the elderly patient is treated with an antidepressant. In the concomitant use of these two drugs the patient should be carefully monitored for any symptoms of serotonin syndrome. They include, for example, anxiety, restlessness, hyperactivity, sleeplessness, confusion, sweating, tremor, diarrhoea, co-ordination disorders and feverishness (11, 12).

The use of antipsychotics should be limited to a fixed-term treatment of psychosis and severe states of aggressiveness. The response and reactions should be monitored. Cognitive disorders, parkinsonism, akathisia, tardive dyskinesia, sedation and orthostatism are common adverse reactions to these medicinal substances exhibited in the elderly. Long-term use of antipsychotics is commonly considered inappropriate medical treatment (7).

According to studies, loop-diuretics are commonly used for oedema without establishing the cause of the symptom. Their use should be based on a carefully established indication (7).

The importance of selective prescription of serotonin-selective antidepressants is emphasised, because they are mistakenly prescribed to elderly patients suffering from mild states of depression and even to grieving elderly patients (7). There is no proof of their effects in the treatment of mild states of depression or in the improvement of normal states of grief. The use of these drugs has become more common. They are only intended for the treatment of severe or moderate states of depression in conjunction with drug-free therapies (13). The effects of antidepressants should be evaluated at regular intervals and treatment should generally be fixed-term (7).

Duration of use

This section contains instructions for the evaluation of the need for and duration of treatment with certain drug groups, i.e. benzodiazepine derivatives and similarly acting medicinal substances, anti-inflammatory analgesics and irritant laxatives, which are rather commonly inappropriately prescribed for long-term use (7).

Benzodiazepine derivatives and medicinal substances with a similar effect are used as sleeping pills in the elderly, administered every night for several months and even several years contrary to the instructions for use. There is no proof of positive effects of their long-term use in the treatment of sleeplessness. Benzodiazepine derivatives and medicinal substances with a similar effect should not be prescribed for use every night for a period longer than a month. For more long-term use, there should be a special reason (7). Positive effects of drug-free therapies for treating sleeplessness have also been found in the elderly (14). These therapies should be introduced into practice.

To prevent problematic gastrointestinal and other adverse reactions caused by anti-inflammatory analgesics, their daily use should be restricted to a course of treatment lasting for a maximum of three months. For the treatment of long-term pain, the primary prescription should consist of paracetamol (7).

Long-term use of irritant laxatives may cause paralysis of the intestinal wall muscles and paradoxical constipation. Their use should be restricted to three weeks. The treatment of constipation in elderly patients who have suffered a stroke or who have Parkinson's or some other severe neurological disease, may require treatment for a longer period (7).

Dosage

The recommendations include those for daily maximum doses of some antipsychotic drugs. Exceeding these maximum doses will increase the risk

of adverse reactions without increasing the positive therapeutic effects. The doses of antipsychotic drugs are established individually once the symptoms and the circumstances of the patient have been stabilised by treatment (7).

Multiple drug treatment

It is considered that the concomitant use of some medicinal substances of the same ATC Code should be avoided. The problems arising from the concomitant use of two or more benzodiazepine derivatives or medicinal substances with a similar effect, two or more antipsychotic agents, two or more anti-inflammatory analgesics or two or more opioids, are emphasised because of the increased development of adverse reactions without the increase in positive therapeutic effects (7).

Medicines to be avoided in the treatment of certain diseases

It is emphasised that the use of an anti-inflammatory analgesic in the treatment of arthrosis should be avoided if the efficacy of paracetamol has not been tried first. Opioids should only be prescribed if paracetamol or an anti-inflammatory analgesic has been found ineffective (7).

Elderly patients with dementia easily suffer from adverse CNS effects caused by drugs. They should not be prescribed potent anticholinergic agents or long-acting benzodiazepine derivatives. The use of other benzodiazepine derivatives, substances with a similar effect and other sedatives should also be restricted. It is emphasised that antipsychotics should only be used for the treatment of psychotic symptoms or severe states of aggressiveness. The doses should be kept to a minimum, the effects and adverse reactions evaluated at set intervals and the use should not be continued for several years (7). The psychotic symptoms and aggressiveness in many elderly dementia sufferers are cured with the use of antipsychotic drugs for a couple of months (15).

Finnish examples of medical treatment

The use of benzodiazepines with a long half-life and potent anticholinergic agents is common. The concomitant use of two or more benzodiazepine derivatives or a substance with a similar effect, and the concomitant use of three or more antipsychotic agents, are a reflexion of the problems associated with medical treatment of the elderly in Finland (16, 17).

What should be done?

Finland needs recommendations for the medical treatment of the elderly based on the expertise and critical views of experts in the field of geriatrics, clinical pharmacology and clinical pharmacy. Further training in the medical treatment of the elderly should be arranged for doctors and other health care employees. Increase in the training of geriatricians and the establishment of departments and units of geriatrics at the university and central hospitals is necessary. Offices of experts in clinical pharmacy should be established at hospitals. Data systems containing reports of drug interactions should be introduced at all health care institutions and pharmacies throughout the country. The data systems should be developed to incorporate the availability of reports of the parallel use of drugs and the use of drugs which should be avoided in the elderly. In the evaluation of renal function in the elderly, a system using serum cystatine C concentration assays should be introduced. Specific guidelines for drug doses appropriate to use in the elderly are also required.

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Summary

Medicines in the focus of health policies

The objective of the working group which has been set up at the National Agency for Medicines in 2005 and is involved in the general planning of pharmaceutical services is to carry out studies and produce reviews in support of decision making and public discussion in relation to pharmaceutical policies.

This survey examines the impact on pharmaceutical policies of the strategies developed in Finland within the administrative sector of the Ministry of Social Affairs and Health and compares them with the corresponding policies in the other Nordic countries and the EU. The survey serves as a background review for the working group.

Pharmaceutical policy 2010, a document published by the Ministry of Social Affairs and Health in Finland in 2003, was the first distinct policy document discussing the aims of the pharmaceutical sector. Among the objectives and schemes of the Ministry during 1988–2003 pharmaceutical services were discussed merely as a restricted part of the health care system, despite the continuously increasing significance of drugs in both the treatment of diseases and of symptoms, and the costs involved.

In their health and drug policies the Nordic countries have several similarities. Key topics within health care include the public health protection and promotion and the increasing costs of drugs. Drugs are usually discussed as a separate issue with primary focus on costs and ways of reducing them. In Finland the proportion of drug costs amounted to almost 16% of the total health care costs in 2003.

At the EU level particular cause for concern is created by the declining innovation and competitiveness of the European pharmaceutical industry overall, and also by the introduction of free internal markets in the medicinal products sector. The important role of the pharmaceutical industry in maintaining European competitiveness has also separated the pharmaceutical policy from the general health policy.

In the light of health policy documents, drugs and pharmaceutical services in Finland appear to occupy a conflicting position. The continuous increase in drug costs poses a health political problem. On the one hand, economic advantages can be created with drugs in the rest of the health care sectors, e.g. reduction in personnel costs. This may, on the other hand, conflict with the aims associated with improving the welfare and relative status of disadvantaged population groups.

Various cost management methods include supervision of drug pricing processes, the principles of the drug reimbursement system and the monitoring and guidelines associated with prescribing. Pharmacotherapies and pharmaceutical services should in future be viewed as an integrated part of the health care system because, if wisely managed, pharmacotherapies can in fact reduce the total health care costs. Great expectations are at present attached to the monitoring and guidelines of drug prescription. It appears nevertheless that drug cost problems are continuously becoming a major concern with regard to the multi-channel financing system of drugs and in the discrepancies among its various parts.

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Nitrofurantoin and pulmonary adverse reactions

Nitrofurantoin is widely used because it works well in the context of microbial resistance and is cost-effective in the prophylaxis of urinary tract infection. In the Finnish Current care guideline (from the year 2000) for urinary tract infections, nitrofurantoin is recommended as the primary therapy in cystitis, alongside trimethoprim and pivmecillinam.

Judging by the literature, the most common adverse reactions caused by nitrofurantoin include gastrointestinal symptoms (nausea, abdominal pain and diarrhoea). Skin symptoms are estimated to have occurred in 1–2% of patients treated with nitrofurantoin, and other reactions indicative of hypersensitivity reported have included drug fever and occasionally anaphylaxis. Adverse liver effects (increased liver values and hepatitis) are relatively rare. Large doses have occasionally been associated with polyneuropathy (90% of these patients have suffered from renal failure). Isolated cases of benign intracranial pressure have been reported, and the most common CNS symptoms have included headache and vertigo. Blood count changes and haemolytic anaemia are also a possibility.

Nitrofurantoin causes acute pulmonary damage more often than any other drug. About 90% of the pulmonary reactions are acute. The severe acute form is estimated to have occurred in one patient per 5,000 prescriptions. In long-term users, one in 750 patients is estimated to develop a chronic pulmonary reaction so serious that the patient is hospitalised due to the disorder. The acute form occurs typically in women at the age of 40–50 years, whereas the chronic reaction is more common in older patients.

An acute pulmonary reaction caused by nitrofurantoin is independent of dose, and the symptoms occur within a couple of hours or days of the start of the therapy. The symptoms include fever, dyspnoea and cough, possibly associated with skin rash. Chest pain and cyanosis may also occur. Blood leukocytosis and eosinophilia are common, and the CRP may also be elevated. Pulmonary imaging may show alveolar or interstitial infiltration; pleural effusion may also be present.

A chronic reaction develops following weeks or years (often more than half a year) of using the drug. Dyspnoea and cough are also symptoms of a chronic reaction, with the added symptoms of tiredness and a declining general condition. Pulmonary imaging usually reveals bilateral diffuse infiltration in the basal segments, but eosinophilia is not usually present in the blood differential count. Testing for the rheumatoid factor or antinuclear antibodies may be positive. A chronic reaction may be more difficult to recognise because of the slow development of symptoms, and the patient's treatment, possibly long-term, is not readily suspected. Cases of death have been reported, associated with both acute and chronic reactions. BOOP (i.e. cryptogenic organised pneumonia, COP) may also be associated with the use of nitrofurantoin. Other types of pulmonary damage have also been described, e.g. rare cases of alveolar haemorrhage (www.pneumotox.com).

Case 1.

Acute pulmonary reaction

A 28-year-old female, otherwise healthy except for recurrent urinary tract infections, was hospitalised in the 30th week of pregnancy, having been admitted from a maternity clinic due to fever and dyspnoea. A week prior to the incident she had been started on nitrofurantoin therapy for urinary tract infection. On arrival her general condition was good, and auscultation of the lungs revealed nothing out of the ordinary. The blood count showed leukocytosis, but no eosinophilia. Elevation of the CRP was also present; 132 mg/l. The findings on pulmonary imaging were scarce, but the contour of the heart at the apex of the right medial segment was indistinct.

Nitrofurantoin-induced pulmonary reaction was suspected clinically, since dyspnoea associated with the use of nitrofurantoin had occurred in the patient previously. Infection was nevertheless also suspected and the patient was hospitalised. The therapy consisted of a single dose of 40 mg methylprednisolone intravenously combined with antibiotic treatment. Nitrofurantoin was discontinued. Dyspnoea abated quickly and fever also dropped within 24 hours. Three days from the start of treatment, the CRP fell to 45 mg/l and the patient was discharged symptom-free; cefalexin therapy was continued for another 10 days. In this patient, the symptoms (fever, dyspnoea) are indication of an acute pulmonary reaction caused by nitrofurantoin, so is dyspnoea which occurred earlier in association with the use of this drug. With an atypical pulmonary imaging finding and absence of eosinophilia, and also symptoms and findings indicative of an infection, the diagnosis remains nevertheless slightly uncertain. Nitrofurantoin was not recommended thereafter.

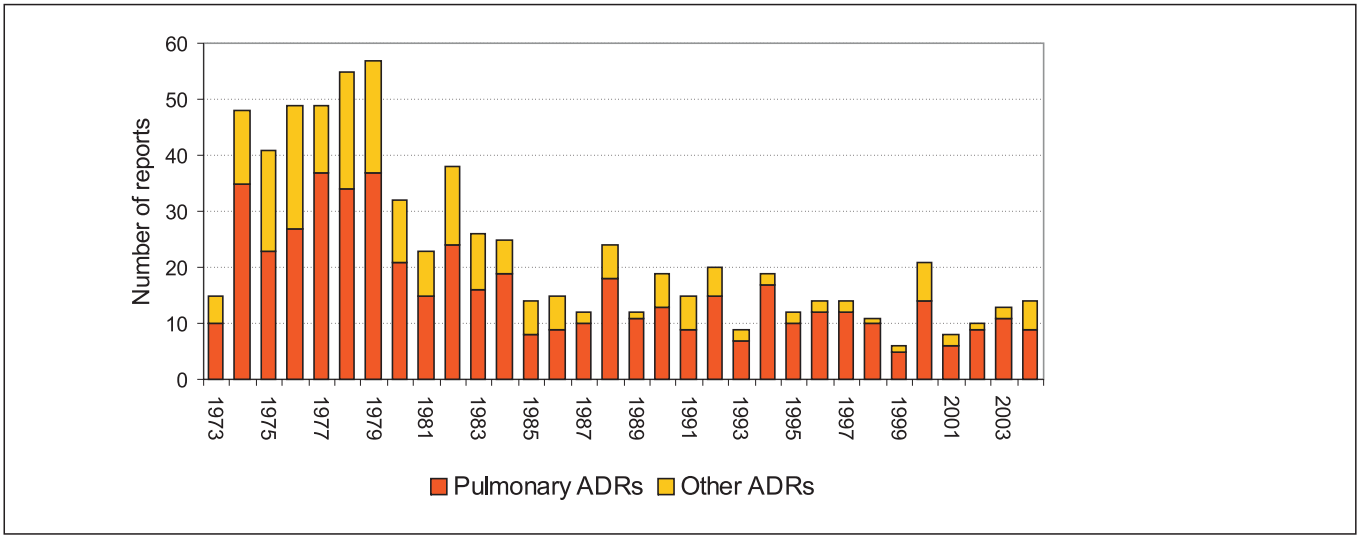

Fig. 1. ADR reports associated with the use of nitrofurantoin in 1973–2004

Case 2.

Chronic pulmonary reaction

A 77-year-old male with hypertension, coronary artery disease, paroxysmal atrial fibrillation and prostate cancer, was given nitrofurantoin as prophylactic treatment for urinary tract infection (the patient has had a percutaneous catheter in the urinary bladder for a number of years). The medication consisted additionally of Emconcor 5 mg x 1, Primaspan 100 mg x 1, Diovan comp x 1, Ismox 20 mg x 1, Casodex 50 mg x 1, Norvasc 5 mg x 1 and Procren injections every 12 weeks. After about four months of nitrofurantoin therapy (75 mg x 1) the patient was transferred from a health centre to a hospital due to a dry cough and intermittent fever that had lasted for a week and a half. The symptoms had been treated with antibiotics without a response. The general condition was beginning to decline. Pulmonary imaging showed extensive predominantly basal infiltratations bilaterally. An HRCT study showed changes which could have been indicative of a chronic reaction to a drug, for example; some ground-glass opacities, peripheral subpleural consolidations, and interlobular interstitial thickenings, with a little pleural fluid bilaterally. Blood tests revealed elevated ESR (95) and CRP (118 mg/l). Leukocytosis, anaemia or blood eosinophilia were not found. On arrival at hospital that the patient was clearly hypoxaemic (aB-pO2 6,6 kPa) and in need of supplementary oxygen. Nitrofurantoin was discontinued, and due to severe dyspnoea the patient was given intravenous methylprednisolone 40 mg x 3 for two days, followed by predisolone 40 mg/day orally. Antibiotic therapy was given for 24 hours intravenously, followed by oral administration for one week. After 5 days of treatment in hospital the patient felt better but was still suffering from breathlessness and needed supplementary oxygen. CRP had fallen to 22 mg/l, and the patient had no fever. Cortisone therapy was continued for a total of four weeks reducing the dose decrementally, and the patient was transferred back to the health centre from where he was later discharged. A follow-up appointment two months later showed clear improvement in condition, even though dyspnoea was still present on exertion. On pulmonary imaging the changes had clearly thinned out, and the hypoxaemia had also been relieved (aB-pO2 10.4 kPa).

Nitrofurantoin in Finnish ADR data

The adverse drug reaction register was processed for reports associated with the use of nitrofurantoin over a period of 32 years. During that period, nitrofurantoin had been reported on 740 occasions (4% of all reports, the total number being 18,923). The reports peaked in the 1970's when the proportion of reports on nitrofurantoin varied between 8% and 13% of all reports, declining relatively evenly down to a variation of between 1% and 3% in the 2000's. Females were involved in 680 of the reports and males in 60, reflecting the user group of nitrofurantoin. Of all the patients providing the material 394 were over 65 years of age (53%). Four reports involved patients under the age of 10, all of whom were girls. The youngest of the girls, a 1-year-old, suffered from discolouration of the teeth, a 3-year-old had a rash, a 6-year-old suffered from joint pain and a 9-year-old had developed a pulmonary infiltrate.

Pulmonary reactions

In 1974, in as many as 85% of the reports involving adverse reactions of the respiratory organs the suspected drug was nitrofurantoin, but this proportion has since diminished to between 10% and 18% in the 2000's. Of all the reports on nitrofurantoin, 513 were of adverse pulmonary reactions and the remaining 227 of adverse reactions in other system organ classes. Fig. 1 shows the total number of reports of adverse reactions caused by nitrofurantoin, and the pulmonary reactions among these.

The adverse pulmonary reactions are shown in Fig. 2 with the classification arranged according to the most significant adverse reaction, i.e., if the report involved a pulmonary fibrosis and dyspnoea, the adverse reaction of the report would be classified as pulmonary fibrosis.

The majority of the adverse pulmonary reactions involved unspecified pulmonary infiltration, (268 reports, 16 of which also included eosinophilia in the blood count), while eosinophilic pulmonary infiltration was mentioned in 34 reports. The second highest number of reports received were about pulmonary fibrosis (83), and alveolitis was the adverse reaction

reported in 26 cases. Symptoms alone – cough and dyspnoea, either in combination or alone – were reported on 92 occasions.

Other ADRs

Liver effects were described in 55 of the 227 reports involving other system organ classes (30 reports on pulmonary effects also included a mention of a liver effect), adverse skin reactions were described in 85 reports, and fever was included in 62 reports which did not mention liver or skin reactions. Fever as a symptom was often also mentioned together with other adverse reactions. Among all the reports on adverse reactions caused by nitrofurantoin, 12 mentioned symptoms of polyneuropathy.

Conclusion

Even though the pulmonary damage caused by nitrofurantoin ('nitrofurantoin lung') has been known for a long time (the first case in the literature dating back to the 1950's), some of the cases reported to the National Agency for Medicines reveal nevertheless the difficulty of detecting the causal relationship. Patients using nitrofurantoin should be advised to contact a doctor immediately upon detection of symptoms involving the respiratory organs. Nitrofurantoin therapy must in consequence be immediately discontinued. The symptoms of an acute reaction are usually quickly reversed after discontinuation of therapy, but a chronic reaction may result in the development of permanent pulmonary fibrosis. Corticosteroids have been used in the treatment of serius symptoms without controlled evidence of benefit in the (chronic) reaction. In future, nitrofurantoin is of course contraindicated.

The consumption of nitrofurantoin is shown in Fig. 3. The consumption has remained fairly steady during the past 15 years.

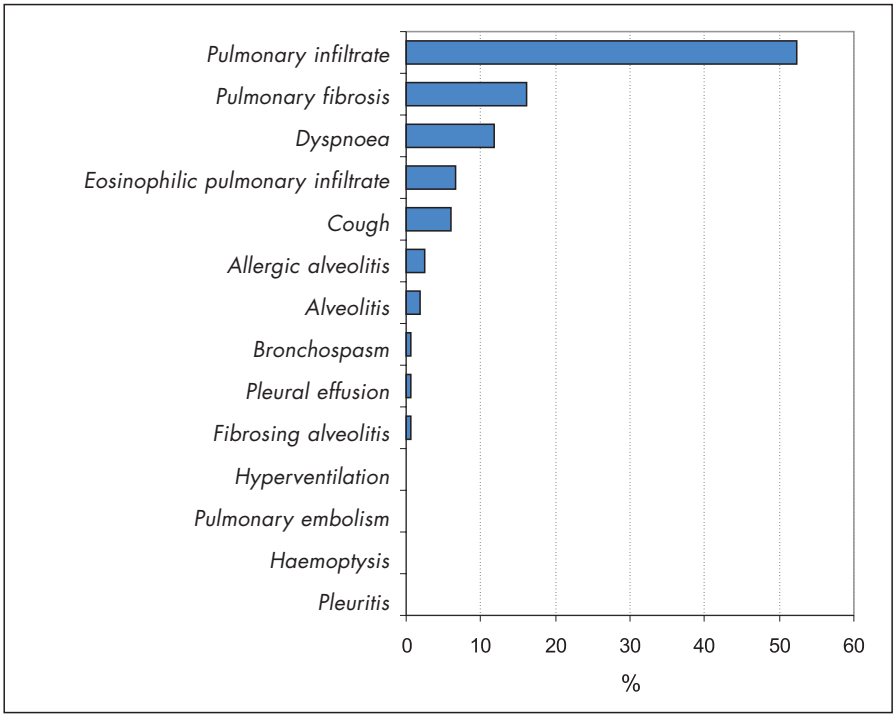

Fig. 2. Adverse pulmonary reactions associated with the use of nitrofurantoin

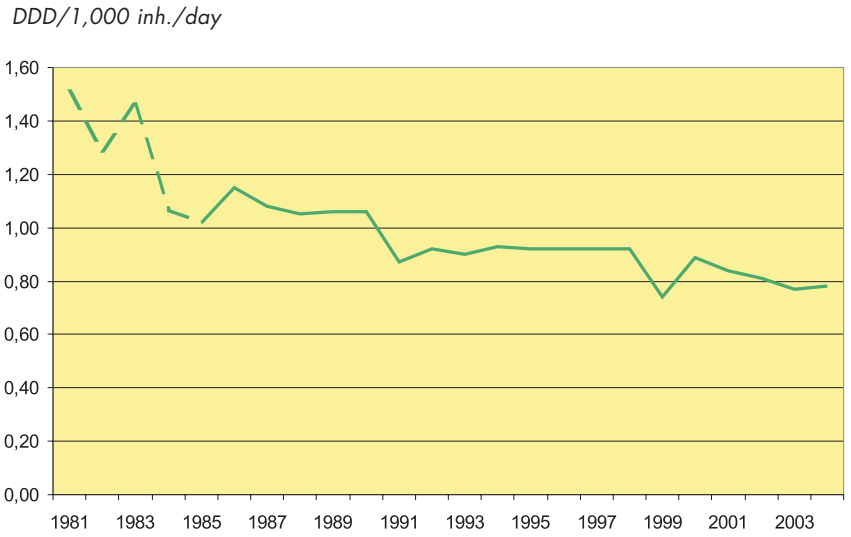

Fig. 3. The consumption of nitrofurantoin in 1981–2004. Figures from years 1981–1984 include only sales from pharmacies.

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Drug presentations and the materials distributed

A considerable proportion of the pharmaceutical industry budget is used for the marketing of medicinal products. It is estimated that the share of drug presentations in the entire marketing budget of a company may be as high as fifty percent (1). Drug presentations are an important and also obviously effective form of marketing, especially in the marketing targeted at doctors. Doctors feel that they are receiving plenty of useful drug information from the pharmaceutical industry, but they nevertheless do not consider that marketing would influence solely their own practices when prescribing (1-8).

In Finland, drug marketing is regulated by the Medicines Act and Decree. According to the Medicines Act, drug marketing should always be based on the approved summary of product characteristics (SPC) of the medicinal product and the information it contains. As with all other aspects of drug marketing, drug presentations should, according to law, disclose all information relative to the drug consistent with its SPC, on the basis of which it is then possible for the individual to have an accurate perception of the composition and medical purpose of the drug.

This study aimed at explaining the extent to which the properties essential to the use of a drug are introduced in the printed material available at drug presentations. Another aim was to find out whether drugs are marketed through the distribution of information which is not based on the approved SPC.

Data and methods

The study was restricted to the actively marketed group of angiotensin-receptor antagonists. All MA holders of drugs of this group on the market were requested to submit the printed material they used at drug presentations during 2003. At the beginning of year, nine medicinal products of this group had a valid marketing authorisation. Six of these, five medicinal products of which had been marketed to doctors, were available on the Finnish market in September 2003. Instead of the trade names letters from A to E are used.

The marketing material used at drug presentations often consists of slide shows, leaflets, dose cards and scientific papers. This study focused only on slides and leaflets handed out to the participants. The factual contents of slides were of particular interest in the study, since the main attention at any drug presentation event is focused on the factual contents of slides, which usually serve as the focal point of details which the companies wish to emphasise in their drugs.

Grounds of evaluation

- How diverse was the presentation of the most essential details of the medicinal product contained in its SPC? The warnings and details of interaction with other medicinal products are the sections of special importance in view of patient safety.
- Studies discussed in the marketing material including, for example, information about new therapeutic indications.
- The association between the medicinal product and the treatment recommendations, and the way in which drug-free treatment was introduced.

A direct comparison was made between the details of the marketing material and the approved SPC, including an assessment of whether the material contained the essential details about the drug.

Results

The marketing material studied consisted, to a large extent, of the demonstration of results of clinical studies. A varied amount of information consistent with the approved SPC of the medicinal products was also disclosed. Comprehensive information about dosing was made available. The indication approved for the medicinal product and the risk factors associated with the use of the drug, however, received minor attention. Table shows the number of properties mentioned in the slides of the medicinal products. It also serves as a general outline of differences between the slide shows of the various drugs studied.

Information consistent with the SPC

Essential hypertension is the therapeutic indication for all the medicinal products studied; the indications for one product also include cardiac failure and the treatment of kidney disease in patients with type 2 diabetes. The slide material of only one product disclosed the therapeutic indication for the drug; the rest of them, except for one, mentioned the therapeutic indication in the abstract of the SPC.

The drug information leaflets of medicinal products included in this study had almost totally omitted mentioning any warnings or drug interactions. The contraindications of angiotensin-receptor antagonists are to a large extent associated with liver and kidney diseases, so the dosages will in any case be especially checked. Even though some of the risk factors were mentioned in the leaflets, they were missing in the slides, which can be considered a shortcoming.

Angiotensin-receptor antagonists have relatively few interactions with other medicinal substances. There are, however, a couple of medicinal substances which in the light of experience in the use of ACE inhibitors are thought to be influenced by angiotensin-receptor antagonists. These substances include, for example, lithium, anti-inflammatory analgesics and medicinal substances with an effect on the potassium concentration. For example, all products of the angiotensin-receptor antagonist group, except one, may according to the SPC increase the plasma lithium concentration up to a toxic level. This effect was not mentioned in

The materials used in drug presentations

Medicinal product	***A***	***B***	***C***	***D1****	***D2****	**E**
Slide shows	*1*	*1*	*1*	*1*	*1*	*1*
Leaflets	*1*	*1*	*2*	*0*	*0*	*3*
Clinical data						
Indications	*1*	*0*	*0*	*0*	*0*	*0*
Dosage and administration	*5*	*1*	*0*	*3*	*0*	*2*
Contraindications	*0*	*0*	*0*	*0*	*0*	*0*
Warnings and precautions	*0*	*0*	*0*	*0*	*0*	*0*
Interactions	*1*	*0*	*1*	*0*	*0*	*1*
Pregnancy and lactation	*0*	*0*	*0*	*0*	*0*	*0*
ADRs	*2*	*0*	*1*	*0*	*0*	*1*
Pharmacological data						
Pharmacodynamic properties	*1*	*0*	*0*	*0*	*0*	*3*
Pharmacokinetic properties	*2*	*1*	*1*	*0*	*0*	*0*
Further details						
Reimbursement status	*1*	*0*	*1*	*0*	*1*	*0*
Packages and prices	*1*	*0*	*1*	*0*	*1*	*0*
Leaflet' date	*0*	*0*	*0*	*0*	*0*	*1*
Total per medicinal product	***14***	***2***	***5***	***3***	***2***	***8***

D 1 = slide show of product D, spring 2003, D 2 = slide show of product D, autumn 2003

the slides of any of the products; the interaction was mentioned in the abstract of the SPC in only one product leaflet.

Angiotensin-receptor antagonists are usually relatively well tolerated (9). The official SPCs of the drugs included in this study also include a mention of the fact the drugs have, according to studies, been as well tolerated as the placebos. As these drugs are not metabolised via the CYP enzyme, this fact has understandably been given little attention.

Details of the price of and reimbursement for all medicinal products were disclosed in some part of the material, but the date of preparation of the leaflet was very rarely included. As the marketing material contained sections (e.g. leaflets) which had been prepared at various times, a date of preparation would make it easier to focus on the most recent changes relative to the product. The Medicines Act also stipulates the obligation of mentioning the date of preparation of leaflets.

Wider therapeutic indications?

The slides and leaflets of all the products included in the study mentioned repeatedly the effect of the drug on the blood pressure. The studies discussed in the leaflets of all products, except one, included this among the approved indications. The leaflet of one product contained an extensive description of a study which had been carried out in patients with cardiac failure. The only approved indication of the product was essential hypertension. The official therapeutic indication was only included in the abstract of the SPC of the product. As the official indication of one angiotensin-receptor antagonist is cardiac failure, the intention was probably to widen the indication of yet another product. The indication has not, however, been approved in the process of granting the marketing authorisation, and marketing of this type is therefore misleading.

Treatment recommendations and drug-free therapy

National Current care recommendations for treatment and drug-free therapies received only very little attention in the material that was studied. The material of two products studied included a separate brochure on current care guidelines for hypertension, but neither the leaflets nor the slides mentioned the national recommendations at all. However, a slide and one brochure of one product included the treatment recommendation of the ADA (American Diabetes Association), which puts the angiotensin-receptor antagonists as the primary choice for patients with type 2 diabetes with hypertension and microalbuminuria. Finnish recommendations for treatment of diabetics with nephropathy (independently of type of diabetes) include either an ACE-inhibitor or an angiotensin-receptor antagonist. Microalbuminuria is considered a sign of developing nephropathy, and consequently, the recommendation is not very far from the Finnish recommendation for treatment, but nevertheless it is preferable to include any national recommendations in the marketing material. To bring up a foreign recommendation for treatment may also be interpreted as an attempt to broaden the user groups of the product in comparison with the national treatment recommendation.

The current care guideline also stresses the importance of drug-free therapy for hypertension (10). In the marketing material under study its mention had been omitted altogether, except for one product. One slide and two brochures of one product stressed the importance of change in living habits.

Conclusions

This study shows that the presentations of essential drug properties in the

marketing material are not adequately varied; they fail to disclose, for example, the indications, warnings and inter-actions. Risk factors, in particular, associated with the use of the medicinal products, were almost totally omitted. Several of the studies introduced were associated with other heart diseases such as cardiac failure, for example, and consequently, these materials fail to give a clear impression of the indication for which the product is officially approved. The positive properties of the products in respect of efficacy and tolerability are extensively discussed, but risk factors associated with the products are hardly dealt with in the material.

The content of drug information given at drug presentations has been the object of some studies ever since the 1970's. The results have been quite similar to those of this current study (11-14). A drug is introduced in a very positive light, but any negative effects associated with the use of the drug are often left without even a mention (15). Adverse effects or contraindications were hardly mentioned at the presentations; however, there are relatively few of them in the drugs of this group. Factors affecting the choice of the correct drug therapy were also touched upon very little at the drug presentations. The marketed drug is presented as the best choice, although this may not in fact be the case. Introductions of drug-free therapies are also very rare (13).

In the light of these studies, the drug information given at drug presentations proves to be inadequate in many ways (13). Safety aspects in particular are often ignored, and should any reference be made to safety it is only done in a way which benefits the marketed product. The information given at drug presentations does, indeed, convey a picture of the drug properties which is too positive (16).

As this study only examined the printed material used at drug presentations, it is not possible to draw conclusions based on it concerning what is being said at drug presentations as a whole. A pharmaceutical sales representative may ignore some of the information contained in the slides, or he or she may verbally quote data which are not found anywhere in the written material. Slides and leaflets are nevertheless very widely used at drug presentation events, and this study is consequently a good starting point for assessing the aspects that a pharmaceutical company wishes to emphasise in its products. Since almost all of the risk factors associated with the use of the drugs were missing in the printed material, it may be assumed that they have not been thoroughly discussed verbally either.

The proceedings at a drug presentation event are naturally influenced by the keenness to participate, or the lack of it, of the doctors present. Doctors are certainly in a position to receive from the pharmaceutical sales representatives good and accurate information also about the risks involved in the use of the products, but this study shows that unless doctors are active themselves the drug marketing targeted at them will be conveyed to them in a very positive light.

For drug presentation events to be of benefit to doctors, the information given at the presentations should be adequately diverse with regard to both the properties of the drugs and the treatment recommendations.

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State Food and Drug Agency from China visits Finnish National Agency for Medicines

In September, the NAM had a pleasure of hosting six delegates from the State Food and Drug Agency. Director General Hannes Wahlroos gave an introduction to the NAM. The other topics of interest included the Finnish pharmaceutical services system and classification of prescription and non-prescription medicines, which were presented by Senior Pharmaceutical Inspector Sami Paaskoski and Senior Medical Officer, Dr. Veijo Saano. After Finland, the delegation was to continue further north to Iceland.

Wahlroos explained the delegation, led by Deputy Director Gao Xiang and Deputy Division Director Yang Ai-Dong, the variety of functions of the NAM.