TABU

Lääkeinformaatiota Lääkelaitokselta

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På svenska

Ledare
35 Strategin styr verksamheten
Hannes Wahlroos

Om biverkningar
36 Renin-angiotensinsystemets hämmare, antiinflammatoriska analgetika och njurarna
Antero Helanterä

37 Spelbegär av Parkisonläkemedel?
Tapani Vuola

Om läkemedelsanvändning
38 Astma och andra obstruktiva lungsjukdomar – läkemedelsanvändningen i Finland år 2004
Terhi Helmiö

41 Naturmedel i rätt och tryggt bruk
Tiina Kostiainen

Om medicintekniska produkter
44 Dentala legeringar och allergi
Robin Lindén

Om läkemedel för djur
47 Utvärdering av veterinärmedicinska läkemedelsmiljörisker
Virpi Virtanen

49 Webblankett för anmälan om biverkning av läkemedel för djur
49 Evira svarar i fortsättningen på frågor om läkemedelsbehandling av djur

In English

Editorial
50 Operations steered by strategy
Hannes Wahlroos

ADR News
51 Interactions of inhaled glucocorticoids – CYP3A4 inhibitors increase the risk of systemic adverse effects
Pertti J. Neuvonen

53 Renin-angiotensin system inhibitors, antiinflammatory analgesics and the kidneys
Antero Helanterä

54 Compulsive gambling due to antiparkinsonian agents?
Tapani Vuola

Drug use
55 Astma and other obstructive pulmonary diseases – drug consumption in Finland 2004
Terhi Helmiö

58 Correct and safe use of natural products
Tiina Kostiainen

Hannes Wahlroos
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Operations steered by strategy

The National Agency for Medicine has recently published its strategy for 2006–2012 available at the website www.nam.fi and posted to the representatives of stakeholder groups in Finland and in the EU collaborative network.

Drawing up strategies is a present-day phenomenon. Several agencies of the social and health care administration such as the National Research and Development Centre for Welfare and Health (STAKES), the National Public Health Institute and the Institute of Occupational Health have recently published their new strategies.

The phenomenon is international, at least in the pharmaceutical field. The European Medicines Agency (EMEA) concluded its own Road Map in December 2004, extending to the year of 2010. The Heads of Medicines Agencies Strategy Paper on the European Medicines Regulatory Network has also been under preparation as well as strategies of many national regulatory agencies.

Working out strategies for NAM has traditions going back a decade. Despite the fact that the supervision of medicines and medical devices is firmly based on the Finnish and EU legislation, a strategy has been necessary. This is important so that resources can be concentrated in a controlled manner precisely on the issues on which special influence is striven for. In particular, European collaboration has in recent years become close and extensive to a degree making it necessary to prioritise the targets of influence in a world of restricted resources.

In its form, the strategy of NAM for 2006–2012 follows the conventional features. It embodies the mission statement, values, definition of clients and description of the operational environment. The vision and strategic targets point the way for future operations.

The statement of the aims envisioned for 2012 reveals that NAM seeks to be a reliable and efficient regulatory authority and a respected expert. NAM has a firm grasp of the pharmaceutical policy discussions. In the EU environment the expertise of NAM is known to its clientele. In its focus areas of influence, in paediatric medicinal products and biological medicines, NAM is the co-operative partner most preferred. NAM also seeks to provide an encouraging working environment and promote the expertise of its staff.

Among its strategic aims I would like to emphasise the importance of the safety and correct use of medicines. NAM aims to develop methods to utilise the existing healthcare register and data resources in pharmacovigilance. The aim is to create preparedness for pharmaco-epidemiological studies which could be set in motion at short notice. The supervision of pharmacies will also be improved, with special attention being focused on the quality and form of drug information and counselling.

With its newly introduced strategy, NAM will continue to develop as a strong and influential partner in the Finnish health care system in safeguarding the safety of medicines and medical devices.

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Interactions of inhaled glucocorticoids – CYP3A4 inhibitors increase the risk of systemic adverse effects

Cytochrome P450 enzymes (CYP enzymes) are important in the metabolism of most medicinal substances. CYP3A4, for instance, is involved in the metabolism of every second medicinal substance. CYP3A4 is also important for the metabolism of many glucocorticoids, but it is nevertheless necessary to recognise that the significance of CYP3A4 varies among the different glucocorticoids.

Among the systemically used glucocorticoids at least dexamethasone, methylprednisolone and budesonide are extensively metabolised by CYP3A4, while this enzyme is of only minor importance in the elimination of prednisone and prednisolone (1-5). CYP3A4 enzyme inhibitors include, for example, several antifungal agents of the azole group, several HIV protease inhibitors, verapramil and diltiazem among the calcium channel blockers, and a number of macrolides (Table). CYP3A4 enzyme inhibitors increase the blood concentration of the systemic glucocorticoids metabolised with the aid of this enzyme up to about 3 to 6-fold, which also significantly increases the effects and risk of adverse reactions of the glucocorticoids. Rifampicin and other enzyme inductors in particular decrease the plasma concentrations of glucocorticoids metabolised by CYP3A4, thereby reducing their effect.

What about the proneness of glucocorticoids to interactions?

Inhaled glucocorticoids such as beclomethasone, budesonide and fluticasone are generally used in the treatment of asthma. Metered dosage produces a good response in the lungs, and due to the low dosage, the systemic adverse reactions of glucocorticoids remain minor. CYP3A4 appears to be an important enzyme in the metabolism of beclomethasone, budesonide and fluticasone. As the bronchial mucous membranes, unlike the small intestine, do not contain significant amounts of the enzyme (6–7), these inhaled glucocorticoids are hardly at all metabolised in the lungs; instead they are absorbed into the blood circulation. But when used orally, budesonide and fluticasone, for example, are extensively metabolised by the intestinal mucous membrane and in the liver, even before reaching the systemic blood circulation, and therefore, when swallowed, their concentrations in the systemic blood circulation remain small and the systemic effects minor.

Only about 10 to 25% of the inhaled drugs reach the lungs, while the main part of the dose remains on the upper respiratory mucous membranes and in the mouth and is swallowed. Glucocorticoid reaching the blood circulation via the lungs is not metabolised until it reaches the liver, whereas the portion of drug remaining in the mouth and swallowed is inactivated in a normal situation mainly by the intestinal mucous membrane and in the liver before ever reaching the systemic blood circulation, thereby failing to cause any systemic adverse effects. The situation is nevertheless radically changed if the patient uses CYP3A4 enzyme inhibiting drugs (Table). Some drugs used in the treatment of HIV in particular and some antifungal agents are potent CYP3A4 inhibitors. When these are used, there can be a manifold increase in the systemic (adverse) effects of inhaled glucocorticoids as their normal presystemic metabolism is inhibited and these agents reach the blood circulation in their active form. The half-lives of these glucocorticoids are also likely to be prolonged, which in itself increases the risk of systemic reactions.

In a clinical trial, healthy volunteers were given alternatively either itraconazole (200 mg/day) or a placebo for five days, followed by inhalations of budesonide on the fifth day of either of these phases. Plasma budesonide concentrations were significantly higher in the itraconazole phase compared with the placebo phase. Exposure to budesonide (plasma budesonide concentration x time, i.e. the AUC value) was increased on average 4.2-fold due to the effect of itraconazole (8). The halting of cortisol excretion occasioned by budesonide was significantly more pronounced in the itraconazole phase compared with the placebo phase.

After this clinical trial was conducted in Finland, itraconazole has been reported to have increased the systemic adverse effects of budesonide in several tens of patients (9–11). A 4-year-old boy, for example, quickly developed symptoms of Cushing's syndrome as a result of the concomitant use of itraconazole and inhaled budesonide (9). All the CYP3A4 enzyme inhibitors mentioned in Table evidently increase the risk of adverse effects from budesonide, irrespective of whether it is used orally, inhaled or via the nasal route. Ritonavir, itraconazole, ketoconazole and voriconazole in particular can be expected to increase the effects of budesonide significantly (12-14).

In addition to budesonide, the use of other inhaled glucocorticoids is evidently also associated with a risk of interaction with CYP3A4 enzyme inhibiting drugs, even though published studies on the fact remain few in number. The oral bioavailability of flu-

CYP3A4 enzyme inhibitors

Ritonavir, saquinavir
Itraconazole, ketoconazole, voriconazole > miconazole ja fluconazole
Telithromycin, erythromycin, clarithromycin
Amiodarone
Diltiazem, verapamil
Ciclosporin
Fluoxetine, fluvoxamine
Grapefruit juice

ticasone, for example, is low due to its extensive metabolism by CYP3A4 during the absorption phase, and hence CYP3A4 inhibitors can be expected to increase the risk of systemic adverse effects of fluticasone. Cases have been published in the literature, in which conventional inhaled or nasal administration of fluticasone has caused Cushing's syndrome in patients on concomi-tant ritonavir therapy (15–16). Consequently, even though studies have been conducted mainly on budesonide, there are justifiable grounds for expecting a similar interaction with inhaled fluticasone and beclomethasone.

Short-term concurrent use of inhaled corticosteroids and CYP3A4 inhibitors lasting for a couple of days is not generally expected to cause significant systemic adverse effects. However, if the concomitant use is prolonged any further, for instance over 1 to 2 weeks, the possibility of glucocorticoid systemic adverse effects should be taken into consideration vis-à-vis all inhaled steroids. It is worth bearing in mind, that in some cases the CYP3A4 inhibitor can be replaced by another one (e.g. itraconazole or ketoconazole with terbinafine in the treatment of fungal infections of the nails or skin). Furthermore, efforts should be made to reduce the inhaled steroid dose. In patients on CYP3A4 inhibitor therapy in particular rinsing the mouth and then spitting out the rinsing liquid after the intake of an inhaled steroid can reduce the risk of systemic exposure to the steroid.

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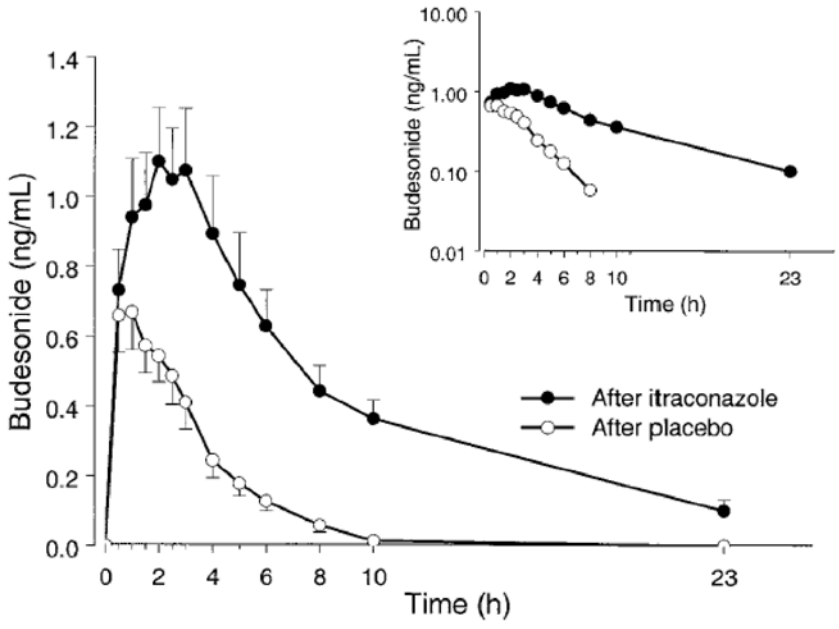

Itraconazole increased the mean total area under the plasma concentration-time curve of inhaled budesonide. n=10 (Raaska et al. 2002).

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Renin-angiotensin system inhibitors, anti-inflammatory analgesics and the kidneys

An elderly patient suffering from arterial disease attends an out-patient clinic after having had a fever for a couple of days. It is discovered that he is dehydrated, there is no urinary excretion, and the plasma creatinine concentration is high. It is also found out that his medication includes renin-angiotensin system inhibitor (angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, the renal effects of which are basically the same). Despite vomiting he has conscientiously taken his medication. It is often only after having been asked about it that he remembers having taken an anti-inflammatory analgesic, because he has believed it to be part of good treatment of fever.

The situation described above is not unusual. Why did the patient's kidneys stop functioning?

Renal effects of renin-angiotensin system inhibitors

Renin-angiotensin system inhibitors are not nephrotoxic, on the contrary, their effects that protect the kidneys are used in the treatment of chronic nephropathy. In certain situations, however, the inhibition of angiotensin II physiological effects will cause impairment of the renal function.

The renal glomerular blood circulation is exceptional: after the capillary network urinary filtration, the blood circulation continues in the artery, in the efferent arteriole. The efferent arteriole is the most important site of impact of angiotensin II in the kidneys. Due to autoregulation, the renal circulation and glomerular filtration remain steady despite even extensive variations in the arterial pressure. This is mainly regulated by the resistance of the glomerular afferent arteriole. The regulation works approximately at a mean arterial pressure of 70 mmHg. As the pressure is reduced below this level, the angiotensin mediated constriction of the efferent arteriole joins in to maintain the glomerular capillary perfusion pressure unless the mechanism is disturbed by medication. In addition to this local compensation mechanism being disturbed, the drug is making the situation worse by reducing the systemic blood pressure.

In addition to the reduced systemic blood pressure, the renal perfusion pressure is also diminished by poor renal circulation as a result of renal artery stenosis, renal diffuse atherosclerosis or cardiac insufficiency. The factors often work together. The situation is of course worsened by the diuretic therapy these patients often need.

Renal effects of anti-inflammatory analgesics

Adverse renal reactions of anti-inflammatory analgesics include acute interstitial nephritis, chronic analgetic nephropathy, fluid retention and hypertension. This case only deals with haemodynamically mediated acute renal insufficiency.

In normal circumstances, adverse renal effects of anti-inflammatory analgesics are unlikely. The circumstances change if the maintenance of renal perfusion pressure is dependent on the effect of vasodilating prostaglandins. These are the circumstances in chronic renal insufficiency and, in the case of healthy kidneys, in water loss and hypotension. Disturbing this compensation mechanism by prostaglandin-synthesis-inhibiting anti-inflammatory analgesic medication can even cause an ischaemic tubular necrosis. Coxibs are in this respect as harmful as conventional anti-inflammatory analgesics.

Interaction

Both a renin-angiotensin system inhibitor and an anti-inflammatory analgesic, either on its own, may provoke renal insufficiency in the situations described above. It should be recognised that the risk is significantly higher if they act together. Their mechanism of action, unfortunately, complement each other in such a situation. As a result of the vasodilating prostaglandin inhibition, the afferent arteriole is not dilated appropriately. And as a result of the angiotensin II inhibition, the efferent arteriole is not constricted as it should be. Thus glomerular capillary perfusion pressure remains too low for the glomerular filtration to work.

The situation is often made worse by a third factor, a diuretic. In an Australian study (Lopoz and Shenfield, 2005) an assay was made as a cross-profile of 301 patients in an internal medicine department in a teaching hospital; their use of a renin-angiotensin system inhibitor, a diuretic and an anti-inflammatory analgesic was studied, including creatinine and estimated creatinine clearance. The use of two or more drugs was markedly associated with renal insufficiency, even though the multivariate analysis took into account the effect of cardiac insufficiency and other diseases associated with the use of these drugs.

In conclusion

Angiotensin inhibitors have justifiably gained their role in the treatment of hypertension and cardiac and renal diseases. Problems could be cut down if intervals of no medication were introduced in water-loss situations. It is important in particular to advise of the risk of concomitant administration of anti-inflammatory analgesics. Understandably, many patients believe the drug to be harmless as it is available without a prescription.

If a problem has risen, it is often, at the initial stage, resolved with a quick infusion of normal saline.

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Compulsive gambling due to antiparkinsonian agent?

A man in his middle fifties was suffering from Parkinson's disease diagnosed as early as the beginning of the 1990s. He had suffered from neurological symptoms in his adolescence. The disease was kept under control for a long time by medication with levodopa/carbidopa + selegiline, but the symptoms became worse at the beginning of 2002, and consequently the medication was changed and pramipexole administered as an adjunct, which at the end of spring had reached the level of 0.7 mg x 3. Efforts were made to increase the dose further due to the symptoms manifested, but as a result of compulsive movements the dose was reduced to the baseline level. The other medication consisted of levodopa/benserazide 100/25 a quarter of a tablet twice a day, and a depottablet for the night and selegiline 10 mg x 1. The motor symptoms were relatively well controlled with these drugs, but in autumn 2002 the patient, had started to gamble and managed to waste his relatively large savings in a short period of time. Pramipexole was replaced by ropinirole, and the urge to gamble disappeared.

There have been about 30 cases in the literature where the patient has acquired a new symptom of compulsive gambling, or where a previous symptom has become worse. It is suggested that its prevalence in advanced Parkinson's disease is as high as 5%. This figure emanates from Spanish material: 12 out of 250 patients suffering from Parkinson's disease fulfilled the disease classification criteria DSM-IV. The suggested prevalence in the normal population is 0.3 to 1.5%.

The symptom is usually associated with the introduction or with the use for a while of dopaminergine/ dopamine agonist. The delay has, however, occasionally been even longer. The drugs frequently mentioned include pramipexole or ropinerole, but the symptom has also been reported, for example, with bromocriptine. In the North-American adverse event reporting system, AERS, the algorithm used for searching for data finds a signal relating to compulsive gambling given for pramipexole, bromocriptine, the combination of carbidopa/levodopa, ropinirole, levodopa alone and pergolide, but none is found for any dopamine antagonist. This confirms the suggestion that dopamine and dopaminergic drugs as a group, cause such a harmful reaction.

In the majority of cases, patients have described the symptoms as appearing during the 'on' stage. It has also been suggested that the symptom could occur irrespective of medication, because a couple of patients exhibited symptoms during stable medication, and reducing the dopaminergic medication did not make the symptoms disappear. This is interesting, albeit somewhat contradictory. The psychiatric symptoms of Parkinson's disease indicate a relative deficiency rather than an excess of dopamine in the pleasure system (depression, anhedonia, apathy, anxiety).

The specific adverse reactions described also include increased sexuality, hypomania and obsessive-compulsive symptoms, with the last two of which compulsive gambling has been associated. The symptom is nevertheless described without a distinct mania or hypomania.

About 15 to 30% of Parkinson's disease sufferers develop dementia, while personality changes and psychoses are also possible, and as a result, various other types of odd behaviour are of course possible. To complicate matters, compulsive gambling while the patient is suffering from Parkinson's disease has been associated with alcohol abuse by the patient, (antiparkinsonian) drug dependence, unnatural jealousy and also depression and anxiety. It has similarly been suggested that compulsive gambling could be an attempt to compensate the hypodopaminergic state of the brain's prize system: gambling would therefore be an external self-treatment for the deficiency in the internal system.

Compulsive gambling is mentioned in the SPC for pramipexole.

The primary treatment is probably a reduction in the dose or a change of medication, while counselling and therapy have also been suggested. Informing the patient's next of kin is definitely recommended. According to one case report, the symptom was successfully treated, but not without adverse reactions, even with risperidone, which of course is an effective dopamine antagonist.

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Asthma and other obstructive pulmonary diseases – drug consumption in Finland 2004

About 5 to 6% of Finns suffer from asthma. It has constantly grown more common over the past 20 years. It is suggested that about 400,000 Finns suffer from chronic obstructive pulmonary disease. In 2004, about 212,117 Finns were entitled to special reimbursement for drugs for chronic pulmonary asthma, and chronic obstructive pulmonary diseases similar to it. For the drugs most commonly used for these diseases, reimbursement was given to 167,904 individuals (1).

According to the classification of the Social Insurance Institution in Finland, the group of chronic pulmonary asthma and similar chronic obstructive pulmonary diseases comprehends asthma, chronic obstructive bronchitis and/or pulmonary emphysema, pulmonary cystic fibrosis, chronic unspecified airways narrowing and its complications, and paediatric bronchopulmonary dysplasia.

According to its severity and need for treatment, asthma is divided into four categories: sporadic, mild, moderate and severe (2, 3). A significant proportion of asthma is mild and needs no daily medication. In the 2004 asthma appraisal, about 48% of anti-asthma drug users were grouped by severity in the mildest category. In accordance with the special reimbursement criterion of the Social Insurance Institution, *pulmonary asthma should be considered a severe and long-term disease, when regular medication has lasted for at least half a year and is still continuing. Because initially effective medication may be followed by symptom-free stages of the asthma, the need for medication should be reassessed from time to time*. Sporadic or mild asthma consequently does not necessarily fulfil the conditions for special reimbursement, or at least not permanently. In accordance with GINA classification of severity, mild or moderate asthma can, nevertheless, be long-term (2).

Chronic obstructive pulmonary disease can be divided into three categories according to its severity: mild (75 %), moderate (requiring medical treatment, 20 %) and severe (requiring hospitalisation annually, 5 %). Drug treatment for chronic obstructive pulmonary disease and other obstructive pulmonary diseases can entitle to special reimbursement on the same principles as drug treatment for asthma.

Treatment recommendations for asthma

According to Finnish and foreign treatment recommendations, the most important primary drug for asthma is an inhaled glucocorticoid (3, 4). According to several comparisons, corticosteroids are considered more effective inflammatory inhibitors than the more recent drugsdeveloped for asthma in particular, such as leukotriene receptor antagon-ists, theophylline or cromones (e.g. 4-6). In some patients, a steroid may in mild asthma be replaced by a leukotriene receptor antagonist or other anti-inflammatory drug.

It is recommended that an inhaled steroid be combined as necessary with an adjunct therapy with a short-acting beta-2 agonist. The need for its use may to some extent be considered an indicator of the inadequacy of the anti-inflammatory medication (3). For persistent moderate and severe symptoms, and for exacerbations, a long-acting beta-2 agonist and theophylline, leukotriene receptor antagonist or oral prednisolone is recommended as an adjunct to a corticosteroid treatment. Some studies have supported a combination treatment of a corticosteroid and a long-acting beta-2 agonist (e.g. 7). In some studies a long-acting beta-2 agonist as adjunct therapy has been found more effective than a leukotrien receptor antagonist when corticosteroid therapy alone is not sufficient (8).

FDA has recommended that long-acting beta-2 agonists should only be used in patients in whom a desired response to other anti-asthmatic drugs, such as a small or a medium dose of a corticosteroid, has not been achieved (9). Despite the fact that the use of a beta-2 agonist has been criticised for its high price, it may occasionally be found to be cost-effective. A number of studies claim formoterol therapy to be more cost-effective than salmeterol therapy (10,11).

In the year 2000, there was fairly good compliance with the national recommendations for treatment in Finland, at least judging by the continuity of treatment and general use of corticosteroids (12). Nevertheless, adult asthma patients had several drugs in use: an average of a total of 4.5 prescription drugs, about 2.4 of which were anti-asthmatics (13). In 2004, the average annual anti-asthmatic drug costs for men were 516 euros and those for women 529 euros (1).

The aims and methods of study

The aim was to determine which prescription drugs were used in the treatment of chronic pulmonary asthma and chronic obstructive pulmonary

diseases similar to it, and how the use and costs of the drugs were divided regionally and socio-economically in the year 2004. Medical treatments were also reviewed on the basis of national treatment recommendations. In March 2006 a new national recommendation for the current treatment of asthma was published, while the drug combinations in the material have primarily been compared with treatment recommendations in force in 2004. The aim of the study was thus to describe how the use of anti-asthmatic drugs in Finland is divided in relation to level of income and education, age, sex, mother tongue and employment.

The study was conducted as a register study using the data of the Social Insurance Institution and Statistics Finland. In this paper, a combination product refers to product which contains an inhaled steroid and a long-acting beta-2 agonist, or an inhaled anticholinergic and a short-acting beta-2 agonist (ATC Code R03AK).

Use of the drugs

The subject material consisted of 92,100 individuals, i.e. 55% of those who were receiving special reimbursement for their anti-asthmatic drugs in 2004. The proportion of women among the subjects was 58%. According to the data, the prevalence of asthma and other obstructive pulmonary diseases was slightly higher in female, older, Finnish speaking subjects living in smaller municipalities than in male, younger subjects, speaking other languages and living in larger municipalities.

The subjects in the study were during 2004 using between one and eleven different anti-asthmatic drugs, a median of 2.3 drugs, which corresponds well with research results presented previously (12). Less than 20,000 individuals (20% of the subjects) used an inhaled steroid together with a short-acting beta-2 agonist. This was also the most common medication in each age group. Furthermore, an inhaled steroid alone, a combination product alone or a combination product together with a short-acting beta-2 agonist, were each used by about 10,000 individuals (about 10% of the subjects). Even here, the divisions into age groups were relatively even. Nor did treatment practices differ between the sexes or the language groups.

The majority of the medications complied well with the treatment recommendations. The fifth most common medication was, nevertheless, a short- or long-acting beta-2 agonist alone without any anti-inflammatory medication for the entire year. About 4,000 patients (4%) were treated in this way. The treatment does not comply with the recommendations, except perhaps for sporadic or mild asthma, when the sufferer sporadically uses a course of steroid, or for sporadic symptoms of chronic obstructive pulmonary disease. In this case there may not necessarily be grounds for special reimbursement for the medication, since according to the treatment recommendation a patient with chronic moderate or severe asthma should continuously use an inhaled steroid. Similarly, in chronic obstructive pulmonary disease with continuous symptoms continuous anticholinergic medication or similar should be used. These 4,000 individuals had nevertheless entitlement to special reimbursement for asthma for about 5 to 6 years longer than individuals who on average had used the four most common medications.

The most common anti-inflammatory medications included an inhaled steroid alone (38% of the subjects in the study), a combination product alone (21%), an inhaled steroid combined with a combination product (6%) and an oral steroid together with a combination product (5%). Almost 5,000 individuals (5% of the subjects) did not use a steroid, leukotriene receptor antagonist or theophylline. A total of 54,000 individuals used an inhaled steroid during the year: 26% of them used beclomethasone, 36% budesonide and 34% fluticasone. Over 3% used several of these products, which is probably explained by the change in medication that took place during the year under review.

Among the bronchodilating medications, the most common ones included a short-acting beta-2 agonist alone (30% of the subjects), a short-acting beta-2 agonist together with a salmeterol combination product (14%) and a salmeterol combination product alone (9%). About 15,000 individuals (16% of the subjects) did not use any beta-2 agonist or combination product.

Drug costs

The annual anti-asthmatic drug costs per person were 533 euros on average (men 529 euros with a median of 368 euros, and women 536 euros with a median of 374 euros, no statistically significant difference). Patients using combination products and/or long-acting beta-2 agonists had the most costly drug treatment.

The anti-asthmatic drug costs were significantly lower (a median of 386 euros) for users of an inhaled steroid compared with those using an oral steroid alone (890 euros) or both an inhaled and an oral steroid (823 euros). This is probably due to the fact that in the milder forms of the disease an inhaled steroid alone is the most commonly used, and the amount and frequency of administration is reduced. Among the inhaled steroid users, the average costs borne by users of beclomethasone were about 350 euros/person/year, budesonide 454 euros/person/ year and fluticasone 522 euros/person/year. Using a leukotriene receptor antagonist and/or theophylline as an adjunct therapy to a corticosteroid added to the drug costs.

On reviewing the drug selection by ATC groups, there were no significant differences between employment situation groups. The anti-asthmatics of pensioners (636 euros/year) were on average more costly, and those of children (262 euros/year), students (384 euros/year) and conscripts/completing civil service (297 euros/year) less costly, on average compared with those of employed individuals (483 euros/year) and the unemployed (510 euros/year). No differences were found in medication or costs between the various levels of education and income.

Use of long-acting beta-2-agonists and combination products

Almost 48,000 individuals (52% of the subjects in the study) were using salmeterol and/or formoterol and/or a combination product containing these.

This was considerably more than the proportion among the subjects in 2000 in the study by Ikäheimo et. al. (13), when long-acting beta-2 agonists or combination products containing them were used by about 30% of the asthma sufferers studied.

Salmeterol and/or a combination product containing it was used by almost twice as many subjects as those who used formoterol and/or a combination product containing it. Both of these long-acting beta-2 agonists were used by over one percent of the subjects. About half of those using a combination product alone were using a combination product of salmeterol and a third were using a combination product of formoterol. The rest were using an anticholinergic combination product containing a short-acting beta-2 agonist or several different products during the year.

The costs of anti-asthmatic drugs were significantly higher in those who used salmeterol and/or a combination of salmeterol (836 euros/person/ year) or formoterol and/or a combination of formoterol (686 euros/person/year) or both (1,111 euros/person/year) than in those who used a short-acting beta-2 agonist or an anticholinergic combination product containing it (277 euros/person/ year), or in those who used no airways-dilat-ating drug at all (210 euros/person/ year). Those, who used salmeterol and/or a combination of salmeterol, and also used short-acting beta-2 agonists or anticholinergic combination products containing these, incurred costs of 932 euros on average, whereas without the short-acting beta-2-agonists the costs were 680 euros. The corresponding costs borne by users of formoterol and/or a combination of formoterol were 800 euros and 576 euros.

In the whole country, combinations of salmeterol (R03AK06) and of formoterol (R03AK07) were used by 28% and 15%, respectively.

A review by districts shows that the use of combination of salmeterol was distinctly more common in all other hospital districts except that of Ahvenanmaa, where 30% of the patients used formoterol and only 1% salmeterol.

The proportion of users of salmeterol (R03AC12) in the whole country was almost the same as that of users of formoterol (R03AC13), about 3%. There were regional differences between the users of long-acting beta-2 agonists. Salmeterol was used more frequently in Länsi-Pohja or Lappi and less frequently in Ahvenanmaa than formoterol.

Conclusion

In the main, the treatment of asthma complied with the national treatment recommendations. Even though the treatment mostly appears appropriate, both under-medication and over-medication are apparent.

The long-acting beta-2 agonist or its combination product was used significantly more commonly in 2004 compared with 2000, and combination products were sometimes used even alongside a separate inhaled steroid or a long-acting beta-2 agonist.

The subjects in the study were on average each using 2.3 drugs, the cost of which was 533 euros per year. The total annual anti-asthmatic drug costs of all 92,100 individuals were about 49 million euros, for which reimbursements were made to the amount of over 35 million euros. The real percentage of reimbursement was therefore about 72%. The highest drug costs were borne by individuals, who used a long-acting beta-2 agonist and/or its combination product.

The medical treatment of asthma did not show significant differences between ages, the sexes, levels of education or income, employment status or the size of the municipality of domicile. There were, however, big differences between the use of long-acting beta-2 agonists and combination products containing them.

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Correct and safe use of natural products

When an entrepreneur introduces a new product on to the Finnish market it is the entrepreneur's responsibility to find out the legislation that covers the product and the legal requirements relating to it and its marketing.

It is not always self-evident which group the product belongs to, since many products may be on the borderline of medicinal products, of cosmetics and of food products. The entrepreneur should in that case seek to clarify the status, for example by submitting an application for classification of the product in the National Agency for Medicines. NAM then makes an evaluation and decides whether the product should be considered a medicinal product.

Medicinal products are required to have a marketing authorisation or to be registered in accordance with the Medicines Act before they are introduced on to the market. Preconditions for a marketing authorisation of a medicinal product are, among others, that it is effective as a medicine and safe for use. The Medicines Act also covers herbal medicinal products with marketing authorisation, traditional herbal medicinal products which ought to be registered, and homoeopathic products. Herbal medicinal products with marketing authorisation can be sold only in a pharmacy. Registered traditional herbal medicinal products and homoeopathic products may be sold even elsewhere.

Natural products and their marketing

The number of natural products on the Finnish market is continuously growing. There is no legislation that covers natural products, while the term is usually interpreted by the consumer to mean either herbal medicinal products regulated by the Medicines Act, or food supplements covered by foodstuff legislation. Only a fraction of products sold in health food shops are registered traditional herbal medicinal products.

According to the Medicines Act, only medicinal products referred to in the Act may be sold as medicines. The foodstuff legislation also prohibits any mention of the foodstuff properties relating to the prevention, treat-ment or curing of diseases. Marketing of food supplements is, however, very varied, and they are often presented with medicinal claims.

NAM does not supervise the introduction on to the market and the marketing of foodstuffs. The supervision of marketing of herbal medicinal products and homoeopathic and anthroposophical products covered by the Medicines Act falls, however, within the remit of NAM.

What is a medicine, and why?

According to the Medicines Act, a medicine has a pharmacological effect or medicinal purpose of use. Section 3, paragraph 3 of the Medicines Act was introduced to clarify the situation relating to the so-called border-line products. When the product fulfils the conditions of definition as a medicine in accordance with the Medicines Act, while it may also be under other legislation, it is the Medicines Act which is primarily applied. Classification as a medicine is product-specific and based besides on the product composition, also on the intended purpose of use, in accordance with the definition of a medicine in the Medicines Act .

Composition and effect of the medicinal product

According to the Medicines Act medicine has a pharmacological, immunological or metabolic mechanism of action, due to which it may be used to modify, correct or restore physiological functions. Classification is typically sought from NAM for products which contain herbs used traditionally in one or other part of the world, and the availability of reliable information about them varies. Classification is often also sought for products which contain a well-known herb, e.g. ginseng or glucosamine, a substance on the medicines list in Finland.

Research results on the pharmacological effects are seldom available of the product to being classified. The evaluation of the product's pharmacological properties is largely based on the information available on the substances contained in the product. The classification procedure takes into account primarily the information supplied by the applicant as well as information available in the scientific literature.

Medicines list

NAM in Finland maintains a medicines list as a guideline. The list is not comprehensive. The list is updated every three years as new medicines are

introduced and as classification decisions are made on medicinal substances. Should a substance not be included in the list, it does not mean that a product which contains the substance could not be classified as a medicinal product.

The substances and herbs included in the list have documented pharmacological properties and are or have been used as medicines. It is likely that a product containing these substances with pharmacological properties will be classified as a medicinal product. The list also contains substances which can be added to foodstuffs, for example, aromatic agents and preservatives. If a product sold as a foodstuff contains substances included in the list, the use of the product should be based otherwise than on its pharmacological effect.

Medicinal use

Medicinal use according to the Medicines Act includes prevention, alleviation or curing of diseases or their symptoms. A product which, based on its pharmacological effect, is used in attempts to modify the physiological functions, also has a medicinal use. The name of the product, package information text, presentation and intended purpose of use and the marketing material are issues on which the evaluation by NAM as to whether the intended use of the product is medicinal is made.

It is likely, in our Internet era, that a consumer will be looking for products and product information abroad. The classification procedure therefore also takes into account the marketing of the product in other countries. In the evaluation of product presentation, the image the consumer is likely to acquire concerning the product is essential.

Medicine

A product classified as a medicine may not be for sale as a foodstuff. Before the medicinal product is introduced on to the market, a marketing authorisation or registration must be applied for. At this stage of an application relating to herbal medicinal products it is determined whether the product fulfils the preconditions of the Medicines Act set for traditional herbal medicinal products or whether it should be considered a homoeopathic product.

A product classified as a medicinal product is not automatically granted marketing authorisation or registration. The application procedure for marketing authorisation and registration will also establish whether the product fulfils the requirements set by the Medicines Act relating to efficacy and safety, for example.

Not a medicine = a safe foodstuff?

If the outcome of the classification is that the product is not a medicine, according to the opinion of NAM it may be introduced on to the market as something other than a medicinal product. However, a decision on classification is not a pronouncement on the (other) product group that the product belongs to, nor is it a declaration on whether the product is safe to use as a foodstuff.

When assessing the safety of medicines, the risk-benefit balance in the approved indication is essential. NAM is not responsible for the supervision of the safety of foodstuffs. NAM's decision on the classification does not therefore rule out the responsibility of the entrepreneur to ensure that the product complies with another legislation, for example the foodstuff legislation. The entrepreneur is responsible for ensuring that the product, when used in the amount given in the instructions for use, is appropriate as a foodstuff and harmless to human health.

Products on the EU internal markets

Classification is often necessary at the time of import of the product into the country. The issue is often raised about the free movement of goods within the EU internal markets. However, this principle is not applied to medicinal products, and the import of medicinal products is restricted. Restriction of the import of medicinal products and the procedure of marketing authorisation or registration have been considered necessary to protect public health.

The principle of free movement in relation to medicines has been taken into account when drawing up the EU common marketing authorisation and registration procedures. It is the responsibility of the national drug regulatory authorities to evaluate and decide which products are considered to be covered by the Medicines Act. The classification as a medicinal product is not intended to hinder the introduction of a natural product on to the market. Instead, the classification is an attempt to ensure that, prior to its being introduced on to the market, a medicine, whether it is mild or strong, from nature or synthetic, is safe for the consumer to use and is marketed for the approved use.

The definition of a medicine in the Finnish Medicines Act is implemented of an EU Directive. Drug regulatory authorities in other EU countries are also drawing a line between medicines and other products. Further information on the issues is found on the Swedish Medical Products Agency's website (http://www.lakemedelsverket.se/Tpl/NormalPage____3447.aspx) and in the guidebook published by the Medicines and Healthcare products

Regulatory Authority in UK, MHRA, 'A Guide to what is a Medicinal Product' (http://www.mhra.gov-uk).

Collaboration of authorities in Finland

In Finland, the foodstuff products regulatory authority, the Finnish Food Safety Authority (Evira), the customs and the NAM collaborate in respect of the control of border-line products. The drug regulatory authorities and foodstuff regulatory authorities of the Nordic countries exchange data on classification issues and work in collaboration to apply common principles in the classification of border-line products.

The control of foodstuff products marketing will become clearer with the introduction of a Decree on nutritional and health claims which is being prepared in the EU at present. A common practice in respect of marketing of foodstuffs will not, however, change the evaluation of pharmacological properties and medicinal purpose of use, which will remain to be carried out by NAM.

Correct information for consumers

The consumer often has the impression that diseases can be treated naturally and safely with a natural product. Herbal medicinal products are safe to use for the approved indication. The purpose of food supplements is to complement the diet and their effect can be nutritional or physiological. When attempts are made to modify, correct or restore the physiological functions, product in question is medicine.

The entrepreneur has the responsibility for the sale and marketing of the product in accordance with the legislation that covers it. Pharmaceutical professionals play an important role in communicating correct information about the product to consumers. In pharmacies, for example, reliable and expert information is supplied on medicinal products. Pharmaceutical professionals through their training and education, are familiar with the medicines regulation, the development of medicines and the risks associated with the use of medicines. It is professionalism to be able to differentiate a medicinal product and a foodstuff product from each other and to know how to communicate the information to the consumer.

More information on classification
http://www.nam.fi/english/pharma_industry/classification/index.html

Application for classification

Classification should be applied for by submitting a signed written request.

The request for classification and associated enclosures should include:

- name of the product
- dosage form (e.g. tablet, drops)
- comprehensive composition (all the substances contained in the product with quantities given per unit of dosage)
- size of package
- intended purpose of use
- dosage (for adults and children, or possible age restrictions)
- package labelling
- any decision or statement of classification by drug regulatory authorities in another EU country

The application for classification should also include copies of package labelling texts and material used in the marketing of the product.

Full contact information of the applicant should also be given in case of a query for further details.

The application for classification should be sent to

Registry Office
National Agency for Medicines
P. O. Box 55
FI-00301 Helsinki
Finland

The cost of the decision is 85 euros, and the processing time is usually a minimum of 1 to 2 months.

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