TABU

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Medicinal products for paediatric use as NAM's strategic area

There are good grounds in Finland to choose medicinal products for children as the strategic area for focussing on in the EU. Paediatrics has a solid historical tradition in this country. The inheritance of Arvo Ylppö, Archiatrist, the former doyen of Finnish medicine, in the development of research and education in paediatrics and of a network of child welfare centres, is widely recognised. Finnish paediatric research is of a leading international standard. Owing to the well organised uniform education system in Finland, the country has more paediatricians per capita than any other EU country.

The National Agency for Medicines is consequently well equipped for dealing with the increasing challenges imposed by the EU regulatory control in medicines as published in 2005 in the EMEA Road Map 2010. As one of its key measures, the EMEA proposes the setting up of a Network of Excellence of all the specialised national evaluation centres. Specialisation and sharing of work are the prerequisite for the future high-level evaluation of quality, efficacy and safety of medicinal products in the EU. Among the first national drug regulatory authorities, the NAM in 2004 published its own strategic areas of focus in the EU.

The EC regulation on medicinal products for paediatric use will rank as an important historical turning point in the development of paediatric care. The aim of the regulation is to increase the research and development of medicinal products and pharmaceutical forms for children, and to promote the collaboration between the drug industry and regulatory authorities at the administrative and scientific level. The preparation of the regulation is nearing completion, which may be reached in June or in July. The regulatory activities due to the new legislation will challenge the NAM during the forthcoming Finnish Presidency at the end of this year.

The EC regulation on medicinal products for paediatric use includes an obligation to conduct research into these products. During the development of the product, the pharmaceutical company is obliged to present an investigation plan (PIP) to the Paediatric Committee (PC), which will be set up by the EMEA, and to apply for a separate waiver from the requirements if it considers a paediatric use marketing authorisation unnecessary. PIP is a prerequisite for approval of an adult-use marketing authorisation as well.

As a result of the regulation concerning medicinal products for paediatric use, the number of clinical trials in children will increase. To avoid overlapping and unnecessary trials and to safeguard a faster progress in drug development, the regulation includes a proposal for setting up a European paediatric clinical trials network which would combine national research networks and clinical trial centres. In Finland, representatives of paediatric clinics in University Hospitals and the Finnish Paediatric Society, together with the NAM's experts, held discussions towards establishing a national network. The EU network for research of paediatric drugs is expected to be in place and operating during 2007.

The National Agency for Medicines offers excellent opportunities to leading Finnish paediatrics to influence the EU regulatory control of these products. The NAM is actively building up its country-wide network of experts to carry out the evaluation responsibilities of the EMEA. Pharmaceutical companies engaged in the development of medicinal products for paediatric use will benefit from collaborating with the NAM.

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Treatment of acne

Acne is a long-term inflammatory disease, varying in severity, of the sebaceous glands characterised by clogged sebaceous ducts, i.e. comedones, papules, pustules and, in the most severe cases, cysts and follicles. They are typically found on the face, chest and back.

The disease can have a significant influence on an adolescent's quality of life and mental wellbeing – even exceeding the influence of asthma or epilepsy (1). The pathogenesis of the disease is essentially explained by the androgen hormone production in the body, increased production of sebum in the sebaceous glands, hypercornification and clogging of the sebaceous gland ducts, proliferation of Propionibacteria and inflammation of the sebaceous gland and its environs. Hereditary predisposition is a consequential factor especially in the most severe forms of acne. An attempt should be made to target the treatment at as many of the above stages as possible (2).

Diagnosis

The diagnosis of acne is generally uncomplicated. The occurrence of comedones is the cornerstone of the diagnosis. In the absence of these, the differential diagnosis should focus on e.g. rosacea, folliculitis and sebaceous gland hyperplasia. In the planning of treatment of the acne, it is recommended that the degree of severity be determined and recorded. The simplest method of differentiation is that of dermatological changes: 1) comedonal acne, 2) inflamed nodules and comedones, 3) pus-filled nodules in addition to the aforementioned, 4) cysts or follicles in addition to the aforementioned. Development of residual scarring deserves special attention. Milder forms of acne may also produce scarring, in which case more effective therapies should be considered. Further examination is seldom necessary. Polycystic ovary disease ought to be suspected in overweight women with severe or recalcitrant acne, disorders of the menstrual cycle, and dermatological changes indicative of insulin resistance such as *acanthosis nigricans* and abundance of skin tags.

Topical treatment

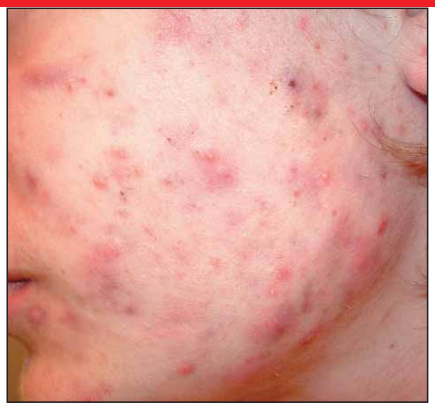
The most effective topical treatment of comedonal acne is a retinoid ointment or gel. The available therapies in Finland include tretinoin cream (0.025% and 0.05%) and adapalene gel (0.1%). The most common adverse effects of topical retinoids are dryness of the mouth and symptoms of irritability, which are more common in our cold climate. Slight redness and scaling are nevertheless associated with the treatment. Acclimatisation of the skin can be accomplished by using a mild strength of the drug at the outset, by applying and leaving the ointment on the skin for only a couple of hours at first, and by having days off the treatment altogether. The ointment should nevertheless be applied to the entire area of the acne and not only to the individual dermatological changes.

Azelaic acid is a comedolytic agent which also decreases the presence of Propionibacteria. The onset of effect is slower than that of retinoids, but it causes less drying and irritation. The available range consists of a 15% gel and a 20% cream.

Benzoyl peroxide effectively decreases the presence of Propionibacteria in the sebaceous gland. It also has a keratolytic effect, i.e. it reduces the presence of comedones. It therefore even works well alone in milder forms of acne. It would appear that benzoyl peroxide is not associated with the problem of resistance development by Propionibacteria. The available treatments include a 4% cream, a 5% gel, and a washing gel which is practical over extensive areas of skin such as on the back and chest. The treatment often causes scaling, dryness and irritation of the skin in the beginning, receding on continuation. It is recommended that the patient be advised at the start of the treatment about the risk of fading in the colours of textiles. Topical benzoyl peroxide is the safest treatment alternative in pregnancy.

The only topical antibiotics available in Finland are clindamycin as a 1% solution and as a 1% ointment. Topical antibiotic therapy should always be combined with a comedolytic therapy, with the course of treatment never exceeding 8 weeks owing to the risk of resistance. The therapy should therefore not be combined with oral antibiotic therapy. Marketing authorisation has recently been granted in Finland to a combined gel of clindamycin and benzoyl peroxide which has proven more effective than either of them alone, with the problem of resistance remaining only a minor one (3).

Comedonal acne



Acne of moderate severity

Very greasy skin with acne should be treated by daily washing with acid washing liquids or cleansing emulsions, but drying antiseptic washing agents increase the risk of adverse effects of topical medical therapies.

Oral treatments

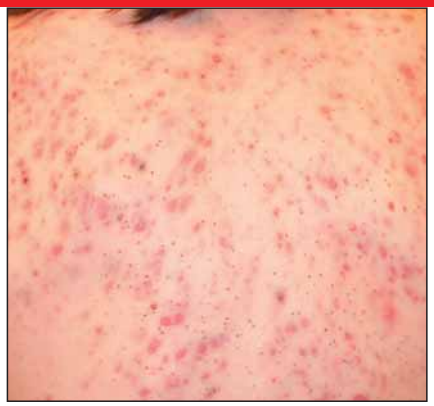
As an adjunct to topical treatment, inflammatory acne of moderate severity also requires internal treatment: antibiotics, the contraceptive pill or antiandrogenic therapies. The first choice antibiotics include tetracycline hydrochloride 500 mg x 2, lymecycline 300 mg x 1–2, or doxicycline 100 mg x 1–2. The most cost-effective alternative is tetracycline. The more recent derivatives produce a quicker response. Stomach complaints associated with erythromycin make its long-term use difficult. Experience in the use of azithromycin and roxithromycin for the treatment of acne is tenuous, with long-term therapy proving costly. Clindamycin should not be used orally in the treatment of acne due to the risk of colitis. Trimethoprim is effective in acne with a daily dose of between 300 mg and 600 mg and should be considered in the absence of other alternatives (4).

The course of treatment with antibiotics should be restricted to 3–4 months but could be repeated if acne is not controlled with a topical treatment. Topical treatment should be borne in mind also during antibiotic treatment, the logical choice being benzoyl peroxide, which reduces the risk of development of resistant bacterial strains. As an adjunct topical retinoids can also be used. In that case it is advisable to use benzoyl peroxide in the morning and retinoid in the evening in order to avoid their inactivating each other.

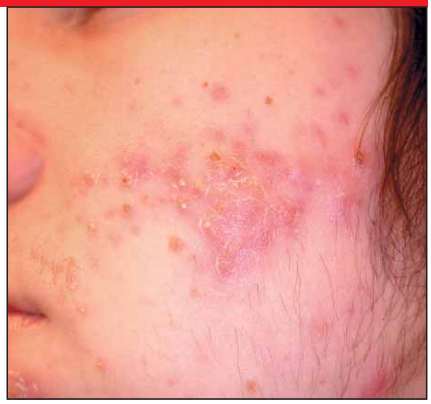
Hormonal therapy is effective especially in women who also exhibit other signs of androgen activity: a syndrome called SAHA (seborrhoea, acne, hirsutism, androgenetic alopecia). A combination of cyproterone acetate and ethinylestradiol has proven to be the most popular contraceptive pill in the treatment of acne. The combination of drospirenone and ethinylestradiol appears to be equally effective but with superior tolerability (5). Instructions to the patient should include the mention of the fact that response to hormonal treatment in acne is not exhibited until after 6 months of treatment at the earliest. Antibiotic treatment in the initial stages, and, in any case, regular topical treatment in addition to a contraceptive pill, may be necessary. There is no convincing proof of reduced effect of a contraceptive pill in association with long-term antibiotic treatment. With the introduction of tighter prescription control for isotretinoin, female patients of fertile age suffering from moderate or severe acne should be offered, more readily than before, an opportunity for hormonal treatment despite there being no need for actual contraception.

Treatment of severe acne

Despite Propionibacteria playing an aetiologic role in acne there is no question of an infection. In severe acne (nodular, cystic or fulminant form) the treatment should be focused on subduing the inflammation. It is consequently often necessary to initiate the treatment by administering an internal corticosteroid (prednisolone 0.5–1 mg/kg) over a 3–6-week period followed by isotretinoin, an oral retinoid with an anti-inflammatory effect. In addition to the reducing effect it has on excessively large sebaceous glands it also effectively reduces the production of sebum and consequently also the quantity of Propionibacteria, and acts as a comedolytic agent. As a result, it exerts an effect at every stage of the pathogenesis of acne, but has no effect on the quantity of androgen hormones. It is recommended that isotretinoin therapy be started with an initial dose of 0.5 mg/kg and be increased as necessary according to response by up to 1 mg/kg to arrive at a total dose of about 120 mg/kg in the course of treatment, which usually produces a long-term response (6). The adverse reactions resemble those of avitaminosis: the unavoidable adverse effects include dryness of the skin and mucosa, especially of the lips, whereas headache and myalgia remain less common. Transient elevation in the serum hepatic enzymes and lipid levels is a possibility and should be checked after 4–6 weeks of treatment. The concomitant use of isotretinoin and tetracyclines should be avoided owing to a possible increase in the intracranial pressure. In studies involving large numbers of patients it has not been possible to show any increased levels of risk of depression or suicide, but owing to idiosyncratic reactions it is recommended that patients with a history of mood problems be monitored more carefully than usual (7, 8). The over-



Severe acne on the back



Nodulocystic acne

whelmingly most important adverse reaction of the drug is its teratogenicity, and, consequently, contraception during treatment and for a month thereafter is absolutely necessary. Half of pregnancies with onset during treatment are spontaneously aborted, over a quarter of the children born manifest visible abnormalities, with an even greater proportion having internal abnormalities or retardation in development.

The European Commission's stricter prescription control was adopted in Finland on 1.3.2005. The drug may still only be prescribed by dermatologists, its supply for women of fertile age is restricted to a 30-day course of treatment on one prescription, and continuation of treatment requires a new prescription which is only valid for seven days. Prescribing by telephone is not authorised. Before the administration of the drug a pregnancy test must be carried out in the laboratory, which should be repeated as necessary during the treatment and a month after discontinuation of the administration. Effective and uninterrupted contraception should be started at least a month before the treatment and continued for at least a month after discontinuation of the treatment. At least two contraceptive measures should be used, the other one of which is a mechanical barrier such as a condom. If the doctor finds grounds to believe that pregnancy is impossible (e.g. hysterectomy, sterilisation), standard prescribing practices apply.

In conclusion

Isotretinoin was already introduced into clinical use over 20 years ago, and despite expectations a safer product has not been introduced since. The drug is nevertheless extremely effective in the treatment of severe acne, and despite uncomfortable adverse effects, motivated patients very seldom discontinue the medication. One abortion necessitated by a certain medication is nevertheless one too many, and conditions introduced to improve the safety are therefore justified. It is noteworthy that the doctor still has the possibility to make an exception from the prescription conditions if he or she has grounds to consider it impossible for the patient to become pregnant. A little scope is still left for the exercise of common sense.

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An injury covered by pharmaceutical insurance

Indemnity clauses of pharmaceutical insurance are discussed, with a presentation of the most common drug groups involved in injuries and the pharmaceutical injuries that have occurred.

The number of new compensation claims for pharmaceutical injury submitted each year is around 220 on average, about half of which are successful in their claim. The majority of the injuries compensated are mild, with only about 12% of the injured parties suffering permanent disadvantage. There has been a slight increase in the number of pharmaceutical injury claims since the beginning of the 2000's, but the relative proportion of injuries entitling to compensation has remained fairly stable from year to year.

A voluntary compensation system for pharmaceutical injuries has been operating in Finland since 1984. The purpose of the insurance is to compensate for the injury (pharmaceutical injury) caused by the medicinal product, after the product has been released for consumption in Finland, and the manufacturer, importer or distributor has subscribed to the insurance. A pharmaceutical injury implies a bodily illness or injury or a comparable severe mental illness which is likely to have been induced by the medicinal product used by the injured party. The insurance will also cover a pharmaceutical injury occurring in a clinical trial if the trial has been conducted in accordance with the regulation issued by the NAM and the company conducting the trial has subscribed to the insurance or the trial is conducted by a principal who has subscribed to the insurance. In accordance with Section 3 of the Medicines Act, a medicinal product means a product intended for human use, blood administered in a blood transfusion or blood products, e.g. red blood cells or thrombocytes, or an intrauterine contraceptive device. It is noteworthy that not all products for sale in Finnish pharmacies are medicinal products complying with the Medicines Act, and not all of them are covered by pharmaceutical insurance; this applies for example to homoeopathic products. Medicinal products released for consumption in Finland mean products that the patients themselves have purchased from a pharmacy, or that they have received in a hospital or other care institute or from a doctor's surgery. An injury caused by medicinal products purchased from abroad or via the Internet is not coverable.

Causal relationship

For a pharmaceutical injury to be coverable by insurance, certain criteria need to be fulfilled. It should at first be determined whether there is a likely causal relationship between the use of the product and the injury sustained. The causal relationship is assessed on the basis of medical knowledge. The assessment also relies on supportive data published in medical publications, and the register of adverse drug reactions and compilations prepared on the basis of these. The most recent data in medical databases is also researched. If the causal relationship is unknown, the injury is not coverable as a pharmaceutical injury. The final assessment of the causal relationship uses a five-stage scale:

Very likely
The highest possible medical proof about the causal relationship; the absence or great unlikelihood of other possible causes

Likely
The injury has several possible causes, but given all the other causes as a whole, the cause in question is the most likely one

Possible
The injury has several possible causes, and the cause in question is not more likely than the rest

Unlikely
The opposite of likely

Very unlikely
The opposite of very likely

Very likely and likely causal relationships fulfil the criteria of an acceptable pharmaceutical injury. It should also be borne in mind that the therapeutic indication of the treatment and its management need to be appropriate for the criteria of approval to be fulfilled.

The coverability of pharmaceutical insurance is also influenced by the degree of severity. An injury may be considered coverable if it has caused a minimum of 14 days of continuous disability or reduced functional ability, permanent illness, bodily injury or death. If the injury remains a minor one, there is no compensation for pain or ache, but the costs and loss of income will be compensated should they exceed the limit of minor injury, which is 85 Euro at present in Finland.

It should then be determined whether the injury is a result of unavoidable risk having been taken during treatment of a severe illness or injury, or whether, given the quality and severity of the illness treated, and given the severity of the injury caused by the medicinal product and the likelihood of occurrence of the injury, for example, the injury should, within reason, be considered a tolerable one. A pharmaceutical injury occurring under these conditions will not be compensated for. An example of unavoidable risk-taking

is where a cancer patient with a poor prognosis contracts agranulocytosis and polynephropathy as a result of cytostatic therapy. Here there is no question of a coverable pharmaceutical injury. An example of an injury which ought within reason to be tolerated and will not be compensated would be weight gain caused by an antipsychotic agent. Inefficacy of a medicinal product is not a pharmaceutical injury. But if the patient's medication or other treatment prescribed has been managed inadequately, or if an error has occurred in the supply of the medicinal product by the pharmacy, compensation for the injury sustained may be applied for from the patient insurance. These, however, are not pharmaceutical injuries.

Pharmaceutical insurance is secondary in comparison with other statutory insurances, and any receivables or payable benefits from statutory insurances or other public funds will therefore be deducted from it prior to payment. The claims procedure follows the standards of the Claims Board for Traffic Accidents. For the assessment of permanent disadvantage accrued, the Ministry of Social Affairs and Health classification of handicaps is applied.

The doctor in charge of the treatment gives his or her own description of the injury by using a separate form. It is desirable that the doctor describes the patient's ability to function, especially following injury, and does it in as close detail as possible. It will be easier for the advisory medical officer to form an opinion of the severity of the injury and the degree of pain and discomfort the patient has suffered, not to speak of permanent disadvantage, if, for example, following damage of the Achilles tendon, a description is given of the patient's ability to move, the analgesics that were needed, the duration of medication, and the length of time that the patient has been on sick leave and normal ability to function has been restricted. If, instead, the doctor's certificate only states: *partial rupture of the Achilles tendon detected by ultrasound*, no conclusions of the kind mentioned above can be drawn and additional reports will be required, and this unavoidably delays the outcome of the proceedings.

Compensation from the Pharmaceutical Insurance Pool should be applied for within three years from the moment when the patient was made aware of the injury caused by a medicinal product, and within ten years at the latest from the time when the administration of the product was discontinued. Every report of an injury is discussed in a group of experts from the Insurance Pool, the members of which include a chief medical advisor, a claims manager, claims lawyers and claims clerks. Compensation criteria are available at the website of the Pharmaceutical Insurance Pool (www.lvp.fi).

The number of the injuries compensated and the most common injuries

In the past five years the number of reports of new pharmaceutical injuries has varied between 162 and 280 a year. Of these, 51–61% resulted in compensation. This number has remained fairly constant since the first days of existence of the insurance.

The highest number of pharmaceutical injuries are caused by the medicinal products most used. Consequently, in 2001–2005, anti-infectives for systemic use (ATC Code J) caused the highest number of coverable injuries, a fifth of all. Drugs acting on the nervous system (ATC Code N) caused 9% of the injuries compensated, quinolone antibacterials (ATC Code J01M) 7%, anti-inflammatory analgesics and antirheumatics (ATC Code M01A) 5% and hormonal contraceptives for systemic use (ATC Code G03A) 4% of the injuries.

The most common pharmaceutical injuries included adverse skin reactions (ca. 10% of all injuries). Some of these consisted of severe skin and mucous membrane damage (mucocutaneous syndrome or epidermal necrolysis), which also frequently led to permanent adverse cosmetic effects. Tendon injuries caused by quinolone antibacterials accounted for 6%, as did liver effects and nervous system effects (e.g. polyradiculitis).

Over 60% of the injuries were mild, resulting in a maximum of one week's hospitalisation or two months' incapacity for work or a reduction in functional ability. Furthermore, the patients recovered fully in more than 80% of the cases, which further supports the interpretation of the injuries as mild. An injury left about 12% of the patients with a permanent adverse effect. Over a period of 20 years, 59 patients have succumbed to a pharmaceutical injury. This means less than 3 deaths a year. The most common pharmaceutical injuries resulting in death included pulmonary fibrosis, pulmonary or cerebral embolism, liver damage, serious epidermolysis or bone marrow damage.

Why have the injuries been rejected?

The most common reason, accounting for 45% of the rejections, was the absence of a causal relationship between the medicinal product and the injury sustained. A fifth of the cases involved an injury which was tolerable within reason or associated with unavoidable risk-taking, and in 15% of the cases the injury remained minor. There were seldom any other criteria for rejection involved.

In conclusion

The pharmaceutical insurance system which has operated in Finland since 1984 guarantees an equal opportunity for all patients to secure compensation for unexpected injury caused by a medicinal product. Both the number of reports of pharmaceutical injury and the number of claims approved have remained fairly unchanged from year to year, even though the number of new reports has somewhat increased since the beginning of the 2000's. About half the reports result in compensation. Since the most important criterion for rejection is the absence of a causal relationship between the product and the injury sustained, a careful consideration of the causal relationship and the compensation criteria would be beneficial to the claimant. It is noteworthy, however, that the number of injuries compensated is totally different from what is from time to time publicly suggested. Furthermore, unlike what is publicly suggested, the majority of the injuries reported have been mild. It may also be possible that some of the incidents caused by medicines – including the more severe ones – remain unreported to the Pharmaceutical Insurance Pool. It is therefore recommended that doctors keep the possibility of a pharmaceutical injury in mind and advise their patients about the insurance available.

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Adverse Drug Reaction register 2005 – some new, some old

It is 40 years ago this year since the National Board of Health in Finland, in the aftermath of the thalidomide catastrophe, started collecting reports of adverse drug reactions (ADRs) into its register. Last year the adverse drug reaction register of the National Agency for Medicines crossed the borderline of 20,000 reports in total, and a new annual record was also reached, with 1,224 reports received. Of these, 657 (54%) were of serious reactions.

ADR reports are received from doctors, dentists and pharmacists. Marketing authorisation holders also report serious ADRs of which they become aware. Adverse reactions associated with intervention studies are not reported to the ADR register. This article deals only with reports called spontaneous, i.e. adverse reactions published in the literature are not dealt with. Adverse reactions caused by vaccinations (92 reports) are also omitted.

The ADR report which can be filled in and forwarded on the Internet has had a good reception. Last year 150 of the reports sent by healthcare professionals were in electronic form. The proportion of electronically submitted reports increased from 3% in March to 36% in November, the proportion in December being 22%. The electronic report form is available at http://hava.nam.fi. For submitting a report, a FiMnet identification code is required. A conventional report form which can be printed out is also available at www.nam.fi.

All ADR reports submitted to NAM are evaluated on a weekly basis at the meeting of experts of the Safety and Drug Information Department. The need for any follow-up measures is judged at the same time. The details submitted are occasionally inadequate for making an assessment, which renders it necessary to contact the person submitting the report for further details.

In 2005 the number of medicinal substances reported on was 333, but on the majority of these only a couple of reports were received. The table lists the medicinal substances which were reported on 10 or more times (a total of 32 substances). The list contains several 'constant favourites' with the anti-psychotic clozapine, for example, having figured in the 1st to 4th position on the list of most frequently reported drugs for the last 10 years, while the number of reports received annually has varied between 21 and 44. As before, the majority of the reports on clozapine (25) this year concerned leucocyte reactions of varying degrees of severity.

On reviewing the list it should be borne in mind that safety of the medicinal substances cannot be compared with one another on the basis of the number of reports submitted. There is a significant variation in the number of users, and drugs in frequent use may be more frequently reported on than those less frequently used. The adverse reactions caused by more recent drugs are probably reported more often than those caused by old and well-known drugs. It may also be that adverse drug reactions which hit the headlines increase the reporting on that specific drug.

Pregabalin and anti-epileptics

Pregabalin (marketing authorisation grated in 2004), is a GABA analogue used in adults for peripheral pain and as an adjunct for partial epileptic seizures.

The ADR reports on pregabalin totalled 41. Half of the patients (20) in these reports were over 65 years of age. Only one used pregabalin for epilepsy; the rest used it for (neuropathic) pain. The daily doses at the onset of adverse reaction varied between 25 mg and 300 mg, and about half of the patients were taking a daily dose of 150 mg.

On review of the reactions considered the most important ones in each report on pregabalin, the nervous system (18 in total) outnumbered the rest. The reactions reported included a reduced level of consciousness (3 reports), muscular cramps (2), vertigo (2), confusion (2), somnolence (2), tremor, memory disturbances, seizures, transient hemiparesis, restlessness, walking difficulties and visual hallucinations. Many of these are well-known reactions listed in the SPC. Exacerbation of cardiac failure, elevation of hepatic enzymes and nausea were each reported twice, while the remainder were isolated single reports.

According to the SPC, in both therapeutic indications the treatment can be initiated with a daily dose of 150 mg, and the dose may be increased gradually up to a maximum daily dose of 600 mg depending on the response and tolerance of the patient. The dose should be adjusted according to creatinine clearance if the patient's renal function is impaired. It may be necessary to reduce the dose for the elderly for the same reason, and caution is recommended at the start of the treatment with, for example, a suggested initial dose of 25 mg twice daily.

The medicinal substances most frequently reported on in 2005

pregabalin	41
clozapine	35
levonorgestrel	25
levofloxacin	25
tamsulosin	24
etoricoxib	22
quetiapine	22
etonogestrel + ethinylestradiol	21
atorvastatin	18
mirtazapin	17
terbinafin	17
zoledronic acid	17
risperidone	17
valdecoxib	16
rosuvastatin	15
infliximab	15
simvastatin	14
bevasizumab	14
capecitabine	13
bupropion	13
insulin glargine	12
ezetimibe	12
isotretinoin	12
etanercept	12
lamotrigine	12
venlafaxine	12
iomeprol	12
norelgestromin + ethinylestradiol	11
ciprofloxacin	11
drospirenone + ethinylestradiol	10
adalimumab	10
valproic acid	10

The antiepileptic drugs next most frequently reported were lamotrigine (12) and valproic acid (10). As anticipated, the most commonly reported adverse reaction caused by lamotrigine was rash (5 reports); among the reactions caused by valproic acid pancreatitis was reported twice, as was granulocytopenia, and the rest of the adverse reactions were each reported once only.

Antipsychotics, antidepressants and bupropion

In addition to clozapine, the list of the most frequently reported antipsychotics included quetiapine (22 reports) and risperidone (17 reports). The most commonly reported reactions caused by quetiapine included elevated hepatic enzymes (4 reports), and granulocytopenia, tachycardia and malignant neuroleptic syndrome, each of which was reported twice. The use of risperidone was also reported to have been associated with 2 cases of malignant neuroleptic syndrome, and hyperprolactinaemia, elevation of hepatic enzymes and rash were reported twice each. Malignant neuroleptic syndrome has also been reported in association with the use of atypical neuroleptics, albeit rarely (Poutanen and Kiviniemi, 2004).

The most commonly reported antidepressants included mirtazapine (17 reports) and venlafaxine (12). Mirtazapine was reported to have caused the following reactions twice or more frequently: leucopenia of various degrees of severity (3 reports), seizures (2) and restless legs (2), and weight gain (2). All of these are known adverse reactions of mirtazapine. The most frequently reported reactions caused by venlafaxin were withdrawal symptoms (4 reports), and skin symptoms (3). One report was received on fatal serotonin syndrome associated with an overdose of venlafaxin.

Bupropion (a non-nicotine aid) was reported on 13 times, on eight of which various skin symptoms (urticaria, rash, folliculitis) were described. Three reports described various nervous system reactions (somnolence, confusion, hypoaesthesia, restlessness, vertigo).

Contraceptives

Levonorgestrel with its 25 reports reached the 3rd place in the most frequently reported drugs list. One of the reports was on minipills and the rest on Mirena, a hormonal IUD. There were 10 cases of unintended pregnancies reported in association with Mirena, four of which were ectopic. The Pearl index of hormonal IUDs (number of pregnancies per 100 woman years) is 0.1 and copper IUDs 0.6. The risk of ectopic pregnancy without contraception is estimated at 1:100, in women using a copper IUD the risk is 1:1,000 and a hormonal IUD 1:5,000 (Heikinheimo and Lähteenmäki, 2004). It is possible that a pregnancy (ectopic) in women using a hormonal IUD is so unexpected that the threshold for reporting is exceeded. Other adverse reactions caused by Mirena are menstrual bleeding disturbances and skin symptoms (2 reports of each), the rest of the reactions being isolated.

NuvaRing (etonogestrel and etinylestradiol), the contraceptive vaginal ring, was reported on in 21 reports in total, 15 of which were about unintended pregnancies. Thromboembolytic incidents were referred to in two reports, as were topical symptoms (cervicitis, vaginal irritation).

Evra contraceptive patch (norelgestromine and ethinylestradiol) was named in 11 reports, 10 of which related to unintended pregnancy and one to deep vein thrombosis. According to the SPC, weight may be an attributable factor for a reduction in contraceptive efficacy in individuals weighing over 90 kg. The weight of the woman who became pregnant was mentioned in only three instances.

There were 10 reports received on Yasmin contraceptive pill, which contains drospirenone and ethinylestradiol. Six of these concerned unintended pregnancies (one a case of blighted ovum pregnancy), three thromboembolic incidents (two of pulmonary embolism) and one a case of elevation of hepatic enzymes.

According to the SPC, studies on NuvaRing demonstrated a Pearl index of 0.4–1.3 in correct use and 0.6–1.7 when incorrect use is also accounted for. The SPC for Evra states Pearl indices of 0.7 and 0.9, respectively. It is possible that the proportion of incorrect use outside any studies is even higher.

The estimated Pearl index of combination contraceptive tablets, when used correctly, is 0.1 and, in typical use, 3 (Heikinheimo and Lähteenmäki, 2004). Forgetting to take the tablet is fairly common, and consequently, the contraceptive efficacy will naturally be reduced. Reports on failed contraception are generally fairly inadequate and do not allow a conclusion to be drawn as to whether the use has been appropriate or not. It may often be the case that the person who submits the report does not know this either.

Antimicrobials

A total of 25 reports on levofloxacin were received in 2005, nineteen of which related to the Achilles tendon: tendinitis (9) and rupture of the Achilles tendon (10), which are well known in association with the use of

fluoroquinolones (Pohjola-Sintonen and Kannisto, 2004). The adverse drug reaction reports on fluoroquinolones totalled 42, of which 26 concerned the Achilles tendon. Damage of the plantar fasciae and a tendon of a digit were reported once each. The rest of the reactions were isolated cases.

Terbinafine was reported on 17 times in 2005, i.e. an unchanged level of reporting compared with the previous year (15). Also similarly to the previous year, the reaction most frequently reported on was the well-known one of loss of taste or taste disturbance (7 reports), with various rashes coming in second place (6 reports). Elevation of hepatic enzymes was reported twice and pancreatitis once.

Tamsulosin

Of the 24 reports received on tamsulosin, 21 described intraoperative floppy iris syndrome. The CHMP's Pharmacovigilance Working Party evaluated this adverse reaction under the leadership of Finland, and the SPCs are at present updated with appropriate warnings inserted in them.

Coxibs

A total of 48 reports were received on coxibs last year; 22 of them concerned etoricoxib, 16 valdecoxib (the marketing authorisation of which is suspended), 8 selecoxib and 2 rofecoxib, withdrawn from the market in autumn 2004.

Of the adverse reactions associated with etoricoxib, 8 concerned various hypersensitivity reactions (such as rashes and mucous membrane symptoms, including one anaphylactic reaction), 7 on the cardiovascular system (one cardiac and one cerebral infarction), and the rest were various isolated reactions. The reports on valdecoxib associated with the cardiovascular system totalled 6 (one cerebral infarction), various dermatological symptoms 5, and liver reactions 2. Among the reports received on celecoxib, facial and oral oedema was mentioned three times and urticaria twice, with the rest of the reactions being isolated (e.g. hepatitis and pancreatitis).

Statins and ezetimibe

The reports on statins in 2005 totalled 53. The majority of them were on atorvastatin (18 reports), followed by rosuvastatin (15) and simvastatin (14). The majority (29) of all the reports on statins concerned muscular reactions of varied severity (mostly myalgia and/or elevation of creatine kinase levels), followed by liver reactions (10). These are very well known adverse reactions related to statins.

Ezetimibe, introduced on to the market in 2003, emerged for the first time on the list of drugs most frequently reported. A total of 12 reports were received, two of which described myalgia and mildly elevated creatine phosphokinase levels in patients with earlier similar symptoms caused by statins. The rest of the reports concerned various reactions, three of which involved the digestive organs and three the skin.

Zoledronic acid

There were 22 reports received on bisphosphonates, the majority of which were concerning zoledronic acid (17 reports). Both zoledronic acid and its adverse reaction most frequently reported, osteonecrosis of the jaw (8 reports), were novelties on the list of reactions most frequently reported. Multiple myeloma was the cause of the treatment in seven of these patients, and advanced cancer in one patient.

Osteonecrosis of the jaw is described in the SPC. The majority of the cases were related to dental treatment, often including infection. Before introducing treatment with bisphosphonates, dental examination and prophylactic dental treatment should be considered, while avoiding invasive dental procedures as far as possible during the treatment.

The Pharmacovigilance Working Party has prepared a class review of bisphosphonates related to osteonecrosis of the jaw. Even though this reaction is especially associated with parenteral bis-phosphonates indicated in cancer treatment, the SPCs for oral bisphosphonates will also be updated.

Immunosuppressive agents

Infliximab was reported on 15 times in 2005, etanercept 12 times and adalimumab 10 times. Infections attributable to tuberculosis accounted for seven of these. A total of 18 reports of tuberculosis infection related to the use of immunosuppressive agents (ATC Code L04AA) were received by the adverse drug reaction register.

Hepatic reactions attributable to infliximab were reported 5 times (one of them being hepatocellular carcinoma) and reactions of hypersensitivity 4 times (one anaphylactic reaction), while tuberculosis infections numbered 3. Two reports of sepsis were received involving etanercept, and these also included bacterial arthritis, while one report concerned tuberculosis infection, one malignancy (ovarian carcinoma) and one an allergic reaction. Tuberculosis infection was the most frequently reported adverse reaction to adalimumab (3 reports; and one case of *Mycobacterium avium* infection), while cerebrovascular disorder was reported twice, oedema also twice and malignancy once (breast cancer).

Antineoplastic agents

A total of 53 reports were received on antineoplastic agents (ATC Code L01). The most frequently reported ones were bevacizumab (14 reports), an angiogenesis inhibitor indicated for the treatment of colorectal cancer, and oral capecitabine (13 reports), a precursor of 5-fluorouracil.

Five of the reports on bevacizumab concerned thromboembolic reactions (3 cases of pulmonary embolism and 2 of venous thrombosis), 3 concerned haemorrhagic complications (epistaxis, melaena and cerebral haemorrhage), while cardiovascular reactions were reported on three times, and intestinal perforation twice.

Four of the reports of adverse reactions attributable to capecitabine were about cardiac reactions, three of which described chest pain. There were reports of granulocytopenia. The rest of the reports were on isolated adverse reactions.

Insulins

Long-acting insulins were reported on 20 occasions. Insulin glargine (12 reports) is a newcomer to the list of the most frequently reported adverse reactions. The majority of the cases were of high blood sugar values (4 reports), three of them reporting a malfunctioning dosing device, and one efficacy problems with the drug. Drug interactions leading to changes in the blood sugar values were reported three times (the suspected interacting drugs were eye drops of brimonidine and betaxolol, enalapril and tramadol). Insulin detemir was reported on 8 times, on most occasions in connection with hypoglycaemia (5) and injection site reactions (2).

Isotretinoin

A total of 12 reports were received of adverse reactions to isotretinoin, which was also a new introduction to the list of the most frequently reported drugs. Deep vein thrombosis was reported twice, and so were elevation of liver values and myalgia or arthralgia. One report described the suicidal thoughts and withdrawal from school work of a 17-year-old adolescent. The connection between isotretinoin and suicide has come under a lot of discussion.

Contrast media

Iodine-containing contrast media are also 'constant favourites'. A total of 45 reports were received, iomeprol being the individual agent mostly reported (12 reports). Almost without exception, the reports on contrast media concerned reactions of hypersensitivity, such as urticaria and mucous membrane symptoms. Anaphylactic shock was described in two reports.

Literature

Heikinheimo O and Lähteenmäki P. Raskauden ehkäisy ja sterilisaatio. In book (eds. Ylikorkala O and Kauppila A): Naistentaudit ja synnytykset, 4. edition. Kustannus Oy Duodecim, Helsinki 2004.

Pohjola-Sintonen S and Kannisto M. Molempien akillesjänteiden repeämä fluorokinolonin komplikaationa. Duodecim 2004;120:975-9.

Report of adverse drug reaction

It is recommended that a report be sent to the NAMs ADR register about all adverse reactions established and suspected, especially when the reaction is serious, an adverse interaction between two drugs is suspected, an unexpected adverse reaction occurs (the reaction is not mentioned in the SPC), the reaction is attributable to a new drug introduced on to the market less than 2 years ago, or when the frequency of the reaction appears to be increasing according to the person who submits the report.

The reactions are considered serious when they have

- resulted in death
- been life-threatening
- caused/prolonged hospitalisation
- caused disabling/incapacitating, or
- caused congenital anomaly/birth defect

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National Agency for Medicines

Correct choice of latex gloves

During the past decade the National Agency for Medicines in Finland has commissioned several studies on the natural rubber allergen contents of latex gloves. The studies have shown that the average allergen contents in the gloves have continuously decreased, except for the past two years. It would appear, however, on the basis of a study conducted in 2005 on the gloves available on the market at the time, that this favourable development has come to a halt, while the differences in the allergen contents are not great. The situation can still be considered good, as 26% of the 84 different types of latex gloves manufactured by 20 companies showed no allergens, and 46% showed only a small allergen content.

In general

Surgical and examination gloves manufactured of latex, i.e. natural rubber, have long been known to cause allergic reactions in their users. The first reactions were detected as early as 1979. The symptoms include, for instance, topical or generalised urticaria, pruritus, excema of the hands, conjunctivitis, rhinitis, asthma, and even anaphylactic shock. The risk groups include extensive users of gloves such as healthcare professionals, especially doctors and operating theatre staff, dentists and dental nurses, users of household and protective gloves, small children with food allergy, atopic individuals, individuals suffering from dermatitis of the hand, and, for example, patients with spina bifida. Sensitisation to natural rubber is diagnosed with the aid of a skin prick test or by demonstrating latex specific IgE-class antibodies in the serum. The presence of allergy is established either by explicit symptoms or by a glove exposure test. During the past two decades, the use of protective gloves has become common as a result of the risk of infectious diseases. Their use has consequently increased the number of individuals sensitised to latex. Studies show that less than 1% of the general population and 3–10% of healthcare professionals in Finland are suffering from latex allergy.

When natural rubber allergy (immediate type I reaction to proteins in the rubber tree latex) was diagnosed in glove users and patients, the manufacturers and authorities took measures to reduce the allergen content in the latex products used in health care. The NAM started to monitor the allergen contents of latex gloves on the market in Finland in 1994. The studies were conducted in collaboration with the National Public Health Institute, Laboratory of Immunology, and Tampere University Hospital, Department of Dermatology. The responsible researchers in the studies were Timo Palosuo, Professor Emeritus, and Kristiina Turjanmaa, Senior Lecturer, Department of Dermatology, Tampere University Hospital.

A commercial quantitative test method (FITkit™) has been developed in Finland for the accurate measurement of allergen content. A comparison of this test and conventional IgE-based methods has shown a highly significant correlation between the total glove extract allergenicity, skin prick test reactivity and the sum of four clinically important latex allergens (Hev b1, Hev b3, Hev b5 and Hev b6.02). This commercial test method was used in the study carried out in 2005. In the test, the allergens dissolved from the glove extracts are captured on to the ELISA plates by monoclonal antibodies. Allergens are determined by specific enzyme-conjugated monoclonal antibodies which react against other structures (epitopes) in the allergen molecules. The standard method used in the six studies conducted previously was the latex IgE-ELISA-inhibition technique. Its use in the present market studies has been discontinued because of the inadequate availability of the type of serum mixture from several latex allergenic individuals in which the required spectrum of IgE-class latex allergen antibodies would be found.

Requirements regarding gloves, and for introducing on the market

Requirements with regard to the safety and suitability for the purpose of surgical and examination gloves intended for introduction into use and on to the market were enforced in 1995, at the same time as the Finnish legislation on medical devices was harmonised with the European Directive. Consequently, manufacturers operating in third countries should comply with the same requirements regarding safety and suitability. Latex glove manufacturing units are in fact mainly found in Thailand, Indonesia and Malaysia, where the producers of the raw material, rubber, are also located.

Compatibility between latex and the tissues, cells and fluids of the body remains a challenge. Extraction of the protein content from the raw material of the glove is problematical, as it is impossible to manufacture latex gloves without the use of natural rubber proteins. However, it is possible to reduce the allergy-inducing protein content significantly by making the methods used during manufacture more effective. The harmful components of the

protein content have been identified, and two of them have been demonstrated as the most important key allergens in natural rubber (Hev b5 and Hev b6.02). Another two allergens (Hev b1, Hev b3) studied with the help of FITkit are significant for patients with spina bifida.

Gloves are required to have good chemical, physical and biological properties. Gloves manufactured from natural rubber have good protective properties, durability and flexibility, and, consequently, despite the risk of allergy, natural rubber remains the most important material for gloves.

The manufacturer should carry out a risk analysis on the gloves, in which the benefits of use should be weighed against the risks. In addition to tissue compatibility, the appropriateness of the agents that come into contact with the gloves and their effect on the material of the gloves should also be assessed.

Lowering of the allergy-inducing protein contents of the gloves takes place at various stages of the manufacturing process. The methods by which the allergen content has been reduced, or allergens removed, should be demonstrated and documented by the manufacturer.

There are no commonly accepted limit values for allowable allergen contents stipulated by the EU. The European Commission Scientific Committee states that the amount of allergens should be made as low as reasonably possible. The methods generally used by manufacturers to measure the amount of soluble proteins only measure the total amounts of protein, not allergising proteins alone, and therefore cannot be used in the determination of a safe level of allergen content.

In practice, however, the risk cannot be removed entirely. Therefore, the package labelling should give the consumer information about the safe use and appropriate storage of the gloves. An EU Commission guide for manufacturers and for notified bodies conducting compliance assessments contains practical advice for risk assessment. It contains guidelines for the management of the manufacturing process and package labelling. It is recommended in the guide that packages of latex containing products should clearly indicate that the product contains latex, i.e. natural rubber, and that the product may cause an anaphylactic reaction in individuals allergic to latex. Terms such as *relatively safe, minimal allergenicity, hypoallergenic* or *low protein content* should not be used because they give an unjustifiable impression of the amount of allergens. The labelling should reveal whether the gloves are prepowdered or powder-free. The packages of prepowdered surgical and examination gloves should include advice to minimise tissue exposure induced by residual powder.

The specific details required to be given about sterile gloves include the date of manufacture, expiry date and method of sterilisation. The packages should include an indicator showing the sterilisation carried out.

It is required in Finland that package labelling should include the information necessary for safe use both in Finnish and Swedish, whereas the rest of the information can be given in English. In the rest of the information given the manufacturers generally prefer to use the symbols set out in standard EN-980.

Results of the glove study 2005

In the glove study commissioned by the NAM in 2005 the allergen levels are classified in five categories. The new classification is based on comparisons with the previous methods. The values of FITkit are given as the total amount of four glove allergens in weight units per one gramme of glove.

The levels are as follows

- **Very low** allergen content (non-measurable, i.e. the total of four allergens is below 0.03 µg/g)
- **Low** allergen content (0.03–0.14 µg/g)
- **Borderline** allergen content (0.15–0.29 µg/g)
- **Moderate** allergen content (0.30–1.14 µg/g)
- **High** allergen content (≥ 1.15 µg/g)

Of the 84 glove types studied 39 were placed in categories 'very low' and 'low'. Of these, 22 gloves had no measurable amounts of allergens. Nearly half of the gloves on the market were included in the low allergen category. The borderline contained 7 gloves and moderate contents were found in 25 gloves. However, there were still 13 types of gloves which exceeded the high content level. Gloves that have moderately elevated or high contents cannot be recommended for use because of the significant health risk associated with their use.

Even though the study involved a specific batch produced by each manufacturer, it nevertheless shows that some manufacturers already in their production apply methods to reduce the allergen contents. It can be assumed that the markets are offering an adequate number of the type of gloves in which the natural rubber allergen content is low to such a degree that they are appropriate for most sensitised and, unknown to themselves, allergic individuals (very low, low). The safest alternative for individuals with diagnosed latex allergy are gloves free of natural rubber and with 'very low' allergen content, of which there are also several types available on the market. Totally latex-free gloves are necessary in healthcare in the treatment of patients with natural rubber allergy.

Nearly all glove packages are marked that *the product contains latex* and serve as a warning that *latex can cause allergic reactions*. This information will guide the latex-sensitised consumer to choose gloves which are totally latex-free. With only a couple of exceptions, the packages of gloves included the required information.

The language requirements in the package labelling information were inadequately fulfilled. The chances of influencing manufacturers in third countries to correct the language in their package labelling are minimal. Stringent national language requirements may lead to otherwise good products being dropped out of the market because of the reluctance of the manufacturer to make amendments for a small market area.

Continuous improvement of quality

Allergen content studies on latex gloves have been conducted in Finland since

1994. Each study has always involved a specific batch of the gloves the manufacturer has had on the market at that particular time. The purpose of the studies has been to monitor the changes taking place in the allergen contents of the manufacturer's gloves when the risk of allergy has been focused on in international studies and study results on allergen contents have been published. The choice of glove plays an important role in the prevention of an increase in latex allergy.

The invitations to tender process ought as a rule include a request that test results of any batch ordered from the manufacturer should indicate the allergen content in the batch.

Comparisons of production quality between manufacturers are difficult with regard to the batch specific study results since the trade names of gloves are frequently changing. Whenever it has been possible, however, uneven product quality of one and the same manufacturer has been detected, and it is therefore not possible to draw any conclusions about reliable manufacturers. There has nevertheless been quite a big improvement in the situation in the past ten years.

There should be several ways of proceeding with the lowering of the latex gloves' allergen contents, some of which would be the development of standards and quality requirements, collaboration between the regulatory authorities in market control, and monitoring of glove production and research.

The publication may be obtained from http://www.nam.fi/english/publications/

NAM reviewed the quality of drug information received by patients

NAM has published a summary of the research carried out into drug information and its quality. The results compiled appear in a review in English, **Drug information for consumers and patients - a review of the research**. The intention is to contribute to the discussion and development concerning drug information both in Finland and on the EU level. The important themes include the sources, methods of distribution, special needs and future challenges of drug information.

The volume of information that patients need about their medication in order to participate in and influence the decision making about their own treatment has increased. The most common sources of drug information are the doctor and the pharmacy personnel. Patients are also looking for information in the package leaflets, on the Internet and in newspapers and magazines. The drug information available varies in quality, however. Good information is often difficult to distinguish from bad.

The review maintains that patients and consumers should be given tools and guidelines for assessing drug information. It should be easy to identify the origin, source and possibly even the financier. Improving the quality and availability of drug information is one of the targets set by the European Union. The European Medicines Agency (EMEA) is constructing a gateway through which reliable and evaluated information about drugs would be delivered to healthcare professionals and patients. In addition, the importance of the national pharmaceutical regulatory authorities in producing and delivering reliable information about drugs would be likely to increase.

The publication may be obtained from http://www.nam.fi/english/publications/

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