TABU

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Lääketietoa Lääkelaitokselta

Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

På svenska | Översättning Mats Forsskåhl

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Editorial

Choices to be made in the regulation of medical devices

NAM's mission statement is to promote the health and safety of the population through the regulation of medicinal products, medical devices and blood products. How can medical devices be effectively regulated where resources are limited? Where should efforts be invested over the next few years? For successful regulation in the medical devices sector and in order to generate the maximum benefit for Finnish health care and patients, certain choices must be made in the evaluation of regulatory targets.

In its inspection duties over the next few years, the Medical Devices Department will concentrate on high risk products, adverse incidents caused by devices, market surveillance, and implementation of the new legislation.

NAM has defined its strategic targets for 2008–2012. Its regulatory strategy is based on impact and risk management. In the continuously changing operational environment, there is a need to be able to predict risks. Identification of risks is especially important when there is a very wide variety of products to be regulated. In the medical devices sector, the situation is precisely that, because the number of products available on the market in that sector totals around 10,000. About a third of these are made by Finnish manufacturers.

In order to achieve the highest possible level of safety for patients, it is necessary to focus resources where there is significant scope to make an impact, and a high probability of risks. In accordance with NAM's strategy, the regulatory and inspection activities of the Medical Devices Department will in future concentrate on high-risk products and on increasing the number of inspections carried out. Examples of high-risk products include cardiac valves, pacemakers, hepatitis and HIV tests and radiation therapy and imaging devices. High risks are also present in the various IT systems in use within health care. Low-risk products typically include disposable hospital accessories, plasters and clinical thermometers.

In addition to regulation, the monitoring of risks and of products which are the cause of adverse incidents also forms an essential part of risk management. The key tools used here include the monitoring and evaluation of adverse incidents caused by equipment; this is carried out using the adverse incidents reporting system. This reporting system makes it possible to monitor and analyse adverse incidents involving various product groups, and to evaluate the risks that these present. It is hoped that electronic reporting will lower the threshold in terms of the decision to submit a report.

The purpose of market surveillance is to oversee the level of safety and degree of compliance with standards of products introduced onto the market. Choosing between different options, correct targeting of resources and active monitoring of markets are also part of market surveillance. The market surveillance programme being prepared will establish how resources are allocated in future years. Products considered hazardous or substandard will be withdrawn from the market in the future, too.

The Medical Devices Department is also involved in the enforcing the new European legislation in Finland. A new Directive amending the Directives on medical devices and biocides was passed by the European Parliament and the Commission in autumn 2007. The amendments involved requirements associated with, for example, compliance with regulations and postmarketing monitoring of devices and accessories. Medical devices introduced onto the market in future will need to be accompanied by more accurate information regarding safety requirements, monitoring and instructions for use.

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National collaborative effort for anticoagulant therapy

In Finland, the practice and monitoring of anticoagulant therapy is decentralised and is mainly the responsibility of those concerned with primary health care. This works well enough provided that efforts are focussed on patient guidelines and practical arrangements for anticoagulant therapy. Unfortunately, this is not always the case in busy environments unless the therapy is made a priority. Unlike in other European countries and the USA, Finland does not have centralised anticoagulant clinics. These clinics have been found to improve the success of anticoagulant therapy in both efficacy and safety, in which case four out of five thrombotic or five out of six haemorrhagic complications can be avoided. Another cost-effective practice is anticoagulant monitoring carried out using self-monitoring equipment. With the patient taking responsibility for the treatment, and when carried out with a systematic approach in selected patients, it decreases the mortality by as much as 30%. Unfortunately, in Finland self-monitoring equipment can be bought by the patient directly from a number of department stores, in which case there is no proof of safety with regard to the patient's suitability for self-monitoring. Such equipment is widely used in home nursing, even though standardised instructions for its safe and reliable use are probably not available. Quality monitoring of the equipment used, sample-taking and results may be neglected. 'Labquality' has shown concern about this situation and established national guidelines for developing the overseeing of self-monitoring equipment.

Standardisation of INR analyses of warfarin dosage

At a layman level one wonders why dosage cards for warfarin almost as a rule show daily variations of doses (e.g. 5 mg and 7.5 mg every other day). By levelling out the dose (taking e.g. 6 mg every day) the patient's memory could be improved and situations where the patient takes a double dose or forgets to take a dose would be avoided. Regular uniform administration benefits the metabolism of warfarin. Further problems are caused by the fact that warfarin is taken in the afternoon and not in the morning together with other medicines. Administration in the afternoon is a result of inapproriate timing of laboratory monitoring. Monitoring of the INR is typically timed to take place on the last day of the dosage programme even though the treatment is prescribed to be long-term and often permanent. The present practice therefore puts the health care centre or private operator – both the laboratory and the doctor in charge of the treatment – under pressure to establish the dosage at once. The management of INR monitoring could be improved by making the INR result available a couple of days before the dosage instructions come to a close, and by establishing the continuation of the therapy electively rather than "acutely". Internationally, computer based INR warfarin doses have been found to be helpful in the management of the therapy. Further improvement could also be seen with a lab result service based on electronic communication or text messaging.

With as many as over 2% of our population are on anticoagulant therapy, mainly warfarin, and with its use increasing by over 10% per year, warfarin is an increasing burden on the national healthcare system. The age of those using warfarin is also increasing especially due to the "epidemic" of atrial fibrillation, and hence the age of 60 years and over is one therapeutic indication for warfarin. A 10-year follow-up study in Cincinnati, USA, showed that the cases of cerebral haemorrhage caused by warfarin increase by as much as 20% especially in the elderly population. Based on what has

Doses to cut warfarin therapy by using two alternative products when INR is above 3.0.

Weight of patient	Cofact	Octaplex
40–60 kg	*30–60 ml*	*1500 IU*
60–90 kg	*60–80 ml*	*2000 IU*
over 90 kg	*80–100 ml*	*2500 IU*

been said above, it is recommended that management of warfarin therapy in Finland be tailored with guidelines.

Warfarin has the largest number of harmful drug interactions

It is doubtful whether warfarin would get marketing authorisation nowadays because of its numerous difficult properties. Warfarin causes the largest number of adverse drug reactions. According to international studies, severe haemorrhages occur in at least 2–3% of patients on anticoagulant therapy every year. Warfarin tops the list of adverse drug reactions occurring in Finland. The most common cases of haemorrhage as an adverse drug reaction are associated with the combined use of warfarin and anti-inflammatory analgesics, some antibiotics and some antifungals (including the topical administration).

The problems with warfarin are caused by its vitamin K dependent mechanism of action and the CYP2C9 route of metabolism, and severe drug interactions. A classic case is developed when an infection and associated antibiotic treatment are involved, in which case for example the infection on the one hand increases the levels of fibrinogen and Factor VIII and may intensify the need for warfarin. On the other hand, antibiotic treatment affects the absorption of vitamin K and may cause direct drug interactions (e.g. with metronidazole, which potentiates the effect of warfarin). Acute and chronic inflammatory bowel diseases are also very complicated. A couple of studies published recently show that a regular consumption of vitamin K (the daily requirement is 0.1 mg) puts the reaching of the INR target in balance in patients whose balance of treatment is otherwise difficult to keep under control. More appropriate strengths would also be needed both for warfarin and vitamin K, e.g. a tablet of 1 mg of warfarin and tablets of 0.1 mg and 1 mg of vitamin K.

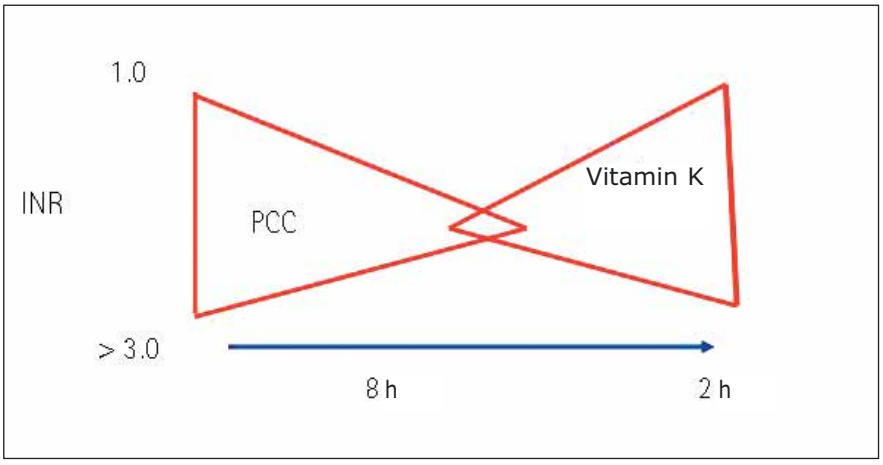

Fig 1. Cutting down on the dose of warfarin in association with severe haemorrhage and procedures which require good haemostasis. Prothrombin complex concentrates (PCC) and vitamin K are administered immediately, and as the effect of PCC diminishes synthesis of the coagulation factors themselves will start.

Cancer patients and invasive measures

All major changes in the adjustment of drug therapy are harmful unless the patient is knowingly being transferred to small molecular heparin injection therapy. This is the recommended procedure for a period of at least 6 months in the treatment of deep vein thrombosis in cancer patients. Irrespective of warfarin, deep vein thrombosis may occur in as many as 10% of cancer patients. Treatment for cancer with associated cytostatic treatment also exposes the patient to cytopaenia and, as a result of radiotherapy and surgery, also to tissue damage. These conditions are difficult to treat in association with warfarin therapy.

Low-molecular-weight heparin is also used in bridging therapy, i.e. in association with major surgery. For this purpose, treatment units should have clear algorithms for the readjustment of anticoagulant therapy, not to mention suppression of treatment, when the indication for surgery is haemorrhage caused by warfarin. With this in mind, two prothrombin compounds (Cofact and Octaplex) with immediate suppressive effect on warfarin have recently been registered in Finland. In emergency situations, e.g. severe haemorrhage or emergency operation, these will be used to restore the clotting system (Table and Fig. 1).

Pharmacogenetics of warfarin

The individual dose of warfarin therapy varies within a 20-fold range. New pharmacogenetic tools are available (HUSLAB, B-VarfaD) for making the introduction of warfarin therapy easier. Polymorphism of CYP2C9 and

VKORC1 explain about 50% of the individual dose requirement. For the pharmacogenetic individual administration there is an algorithm model at the following website: *www.warfarindosing.org*. As a result of some rare (1–3%) polymorphisms of CYP2C9 the dose requirement is minimal and the elimination significantly reduced; pharmacogenetic information detects an individual prone to haemorrhage and will also help in the targeting of other medication metabolised via CYP2C9. Experience should be gained from this new option, and the experience should be brought into proportion with the other factors affecting the patient's proneness to thrombosis and haemorrhage. The most common of these are probably the use of anti-inflammatory analgesics, which impair the haemostasis, and hypertension which has been left untreated or is out of control. Both of these expose the warfarin user to cerebral haemorrhage. I believe that the biggest benefit to start with could be obtained in such patients as are suspected of being at risk of haemorrhage and who have in a year haemorrhages more than 10% of which are severe (*a high bleeding risk index*).

Anything else new in sight?

Extensive efforts have been undertaken to develop new alternative options to warfarin, and there are some within sight in fact – e.g. dabigatran, a direct inhibitor of thrombin, and rivaroxaban, a direct inhibitor of the clotting factor Xa (Fig. 2). These oral anticoagulants will apparently be introduced to the market for short-term prophylaxis of thrombosis as early as this year. However, it will still take years before they are in long-term use, or before they are at least used in the treatment of patients with an artificial cardiac valve. The new drugs have shown antithrombotic efficacy, but the safety of their use will not be established until extensive series of patients and long monitoring periods (a minimum of 18 months) have been gone through. The first direct thrombin inhibitor, ximelagatran, was unfortunately withdrawn from the market immediately before it was due to take the role of warfarin. The reason for the withdrawal was the elevation of liver enzymes detected on long-term monitoring and found in 6–9% of the patients treated.

Conclusion

The circumstances described above are a clear indication that there is a need for monitoring the anticoagulant therapy given, for patient guidelines and for a versatile development. In countries where there are anticoagulation clinics the safety of use and efficacy of anticoagulant therapies have been shown to be distinctly superior in comparison with the decentralised model. The importance of patient guidelines of high quality is emphasised. As air travel is becoming more and more common patients on warfarin therapy need to prepare themselves for the journey, and possibly even for INR monitoring before the return journey as well, since diet and drinking habits probably change while away from home. Patient guidelines include, for example, information about the International Self-monitoring Association of oral Anticoagulated Patients (ISMAAP), an organisation concentrating on patient guidelines. Its present chairman is an internationally renowned researcher on blood coagulation, and this reflects the significant emphasis on patient guidelines.

INR monitoring and dosage adjustment carried out by patients themselves using self-monitoring equipment increases the safety of anticoagulant therapy. With careful patient selection, systematic teaching programme, and the monitoring of equipment and quality, mortality associated with warfarin therapy has been shown to decrease. The responsibility of 'Labquality' includes issues related to the quality monitoring of the screened introduction and follow-up of self-monitoring equipment. All parties interested in safe medical treatment and improved quality in healthcare in Finland should quickly join forces. Safety of warfarin therapy requires national recommendations and centralised efforts.

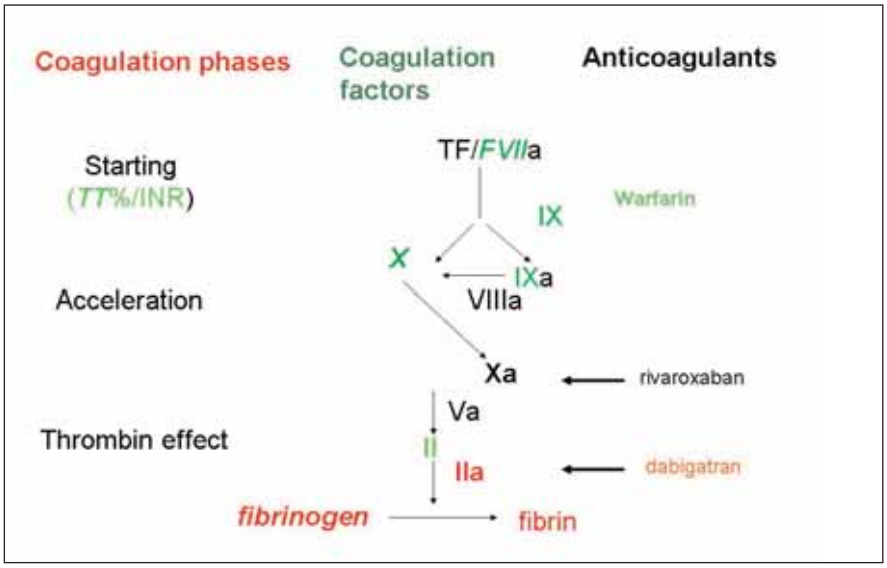

Fig. 2. The coagulation system and relevant anticoagulants.

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Guidelines for the use of high alert medications and monitoring of medication errors in hospitals

International studies have shown that 5 to 10% of patients at some time of their treatment experience some unwanted or unforeseen event which may harm them (5). A high proportion of errors in the patient's treatment are caused by errors in medication.

A medication error is an event, associated with drug therapy, which can lead to a hazardous situation. It may be caused by an action, failure to act, or a situation where the protective measures have failed (6). It is an event which can be prevented, but which, if it is not, can lead to medication which is inappropriate or harmful to the patient, in which case the responsibility for the administration lies with a healthcare professional, a patient or some other consumer (7). About 1% of the patients are assailed by a severe adverse reaction as a result of the irregularity (8, 9).

Special care is required in the administration of medicinal products associated with a risk to the patient of a severe adverse reaction: these are known as high alert medications, since their storage, labelling, reconstitution or administration to the patient require exceptionally good care (10).

In this study information has been compiled concerning the practices in recording of medication errors in central hospitals, and the views of hospital pharmacists on guidelines relating to high alert medications have also been examined. The study has been based on a list of high alert medications assembled up by the American Institute for Safe Medication Practices (ISMP). The list has been updated in 2007.

Procedures

Hospital pharmacists (n=21) in Finnish central hospitals were sent a survey questionnaire by email in the spring of 2006. Pharmacists were asked about the prevailing practices in their own hospitals with regard to guidelines and the supervised use of high alert medications. The regulations and practices associated with these medications were also scrutinised by way of a Table following the ISMP style (Tables 2 and 3). The survey was completed by 11 hospital pharmacists (response rate of 52%).

Results

Monitoring of medication errors?

Active monitoring of medication errors took place in three hospitals and two hospital pharmacies. The monitoring was carried out by using reports (n=2), adverse drug reaction reports (n=1) or other ways specific to the individual department (n=1). In addition to monitoring, an extensive electronic patient record system was going to be introduced at one of the hospitals.

Prevention of medication errors?

The various measures taken to prevent medication errors were described in eight replies (Table 1). The most common measures included setting up of guidelines for the medication practice, providing information about any changes in the range of medicinal products available, and furnishing guidelines for nurses about how to recognise generic medicinal products. Difficulties were found to arise in the recognition of generic medicinal products in patient care, for example when patients were hospitalised. Measures to improve the safety of medication have been introduced in two hospitals.

Monitoring of high alert medications?

When asked about specific means for the monitoring of medicinal products, five hospital pharmacists replied that they did not have in place monitoring focusing on medication risks of the products, and that all medicinal products were monitored equally. The

Medication error is any preventable event which can cause or lead to inappropriate use of a medicinal product or harm the patient when responsibility of the administration lies with a healthcare professional, or a patient or other consumer.

High alert medications are medicinal products conventionally used in medical therapies, but which, when incorrectly administered, expose the patient to inordinately more severe health hazards.

Our study shows that hazards caused by high alert medications can be prevented by taking a number of measures, including for example the extensive use of information technology, increasing the use of ward pharmacies, and developing multi-professional forms of working and methods of medication.

list of high alert medications was filled in by five hospital pharmacists (Tables 2 and 3).

Appropriateness of the ISMP list of high alert medications?

The question about the appropriateness of the list of high alert medications in Finnish hospitals received five replies. A couple of the medicinal products in the list were not considered high alert medications by the hospital pharmacists, and in the case of a couple of others the risk of medication errors was in their opinion also considerably higher. The medicinal products most commonly considered high alert medications included adrenergic agonists, parenteral and chemotherapeutic substances, inotropic medicines, epidural or intrathecal drugs, the liposomal medicinal substances, anaesthetics and opioids, muscle relaxants, intravascular radioactive imaging products and thrombolytics/fibrinolytics. The medicinal products most definitively considered high alert medications included lidocaine, potassium chloride concentrate, potassium phosphates injection, sodium chloride for injection, hypertonic and warfarin. However, dialysis solutions, intravascular sedative medication or oral sedative medication for children were not considered high alert medications (Tables 2 and 3).

The aim of an open question to the participants in the survey was to explore the participants' views on the hazardous properties of various drugs. In two replies the list of high alert medications used in the study was considered too long. It was nevertheless suggested that botulinum toxin, antitoxins and antidotes be included in the list. In one open reply it was also maintained that any specific instructions given on the wards are not always effectively communicated to the hospital pharmacy, nor does the pharmacy know about all near misses occurring with medications.

Conclusions

Medication errors were not systematically monitored in Finnish central hospitals in spring 2006. The conventional record form was found to be a sufficiently good way of recording any medication errors (1, 2, 3, 4). The record is easily converted into electronic form and is appropriate to use for the recording of medication errors and for monitoring of hospital practices.

A process of reporting hazardous events, HaiPro, in order to promote patient safety issues

Table 1. *Prevention of medication errors in central hospitals (n=8).*

Procedure	n
Guidelines for the practice	*3*
Communication about changes in the range of drugs available	*3*
Recognition and review of a generic drug	*3*
Making use of ward pharmacy	*2*
Pharmaceutical education for hospital staff	*2*
Responses to medication errors and near misses	*1*
New practice being introduced	*2*

Table 2. *The views of hospital pharmacists on high alert medications (n=5, x=one reply). The replies are compiled into an ISMP list of high alert medications (12). The list has been updated 2007.*

Medicinal substance	Does this group of medicinal substances belong to the high alert medications in your opinion?		Does your hospital have special instructions for the storage or labelling of this group of medicinal substances?		
	Yes	No	Yes		No
			Storage	Labelling	
Adrenergic agonists, intravenous (e.g. adrenalin)	xxxxx		xx		xx
Adrenergic antagonists, intravenous (e.g. propranolol)	xx	xxx			xxx
Anaesthetic agents in general, inhaled and intravenous	xxx	xx			xxx
Chemotherapeutic agents, parenteral and oral	xxxxx		xx	xxx	x
Hypoglycaemic oral	xx	xxx			xxx
Inotropic medication (e.g. digoxin)	xxxxx				xxx
Cardioplegic solutions	xxx	xx			xxx
Hypertonic dextrose solution (≥20 %)	xxx	xx			xxx
Dialysis solutions	x	xxxx			xxx
Epidural or intrathecal medications	xxxx	x			xxx
Glycoprotein IIb/IIIa inhibitors (e.g. abciximab)	xxx	xx			xxx
Liposomal formulation of drugs (e.g. amphotericin B)	xxxx	x			xxx
Moderate sedation agents, intravenous	x	xxxx			xxx
Moderate sedation agents, oral, for children	x	xxxx			xxx
Narcotics/opiates, intravenous and oral	xxxx	x	x	x	xxx
Neuromuscular blocking agents	xxxx	x			xxx
Radiocontrast agents, intravenous	xxxx	x	xx	xx	xx
Thrombolytics /fibrinolytics, intravenous	xxxx	x			xxx
Parenteral nutritional solutions	xx	xxx	xx	x	xx

has already been developed in Finland (13). Setting up of multi-professional working groups at hospitals would also be ideal; such working groups would regularly analyse any problem situations recorded and develop the general safety of medicines.

If the hospital pharmacy is not informed about problems associated with medications on wards, it is not able to respond to the problems. By using the ward pharmacy or by the setting up of multi-professional working groups in support of patient care, the expertise of the hospital pharmacy could be brought into practice and the safety of medicinal products be improved.

Shortage of time is a big problem in the work of nurses and pharmacy staff. Improving the standard operating procedure (SOP) could probably reduce the workload in patient care and the diversity of the codes. With ward pharmacies the responsibility for the reconstitution of medicines and preparing them for use could become the responsibility of the pharmacist. Increasing the practice of ward pharmacies could also achieve harmonisation of SOP on wards, a reduction in the workload of nurses and an increase in the expertise on medicines among the nursing staff.

In order to improve the safety of medication in Finland, a list of high alert medications appropriate for our practices could be compiled; it would make use of the expertise of hospital pharmacies as well as information received from hospitals about any medication errors, as well as from the National Board of Medicolegal Affairs (17) and about cases of patient injuries.

Literature: see page 15.

Table 3. *The views of hospital pharmacists on high alert medications (n=5, x=one reply). The replies are compiled into an ISMP list of high alert medications (12). The list has been updated 2007.*

Medicinal substance	*Is this medicinal substance a high alert medication in your opinion?*		*Does your hospital have special instructions for storage or labelling of this medicinal substance?*		
	Yes	*No*	*Yes*		*No*
			Storage	*Labelling*	
Amiodarone intravenous	*xx*	*xxx*			*xxx*
Colchicine injection	*xxx*	*xx*			*xxx*
Heparin in injection form, low-molecular-weight	*xx*	*xxx*			*xxx*
Heparin, intravenous, unfractionated	*xx*	*xxx*			*xxx*
Insulin, intravenous and subcutaneous	*xx*	*xxx*			*xxx*
Lidocaine, intravenous	*xxxx*	*x*			*xxx*
Magnesium sulphate injection	*xxx*	*xx*			*xxx*
Methotrexate, oral non-oncologic use	*xxx*	*xx*	*xx*	*xx*	*xx*
Nesiritide	*x*	*xxxx*			*xxx*
Nitroprusside sodium for injection	*xxx*	*xx*	*x*		*xxx*
Potassium chloride for injection concentrate	*xxxxx*				*xxx*
Potassium phosphates injection	*xxxxx*				*xx*
Sodium chloride for injection, hypertonic	*xxxx*	*x*			*xx*
Warfarin	*xxxxx*			*x*	*xx*

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Adverse reactions in year 2007 in Finland

Last year the National Agency for Medicines (NAM) in Finland received altogether 1 174 reports of suspected adverse drug reactions (ADRs), which was slightly more than the year before. There was some alteration in the list of most often reported medicinal substances, but the spectrum of the reported ADRs was greatly similar to the earlier years. 753 (64 %) reports were classified as serious (criteria Table 1), which was a greater percentage than before.

The 1 174 reports included altogether 2 568 ADR symptoms, which means in average 2,4 ADRs for report. ADRs reported on vaccines are not included in this review.

Altogether reports were received for 348 medicinal substances. From 214 medicinal substances there were two or less reports. The medicinal substances for which 10 or more reports were received are listed in Table 2. New medicinal substances on this list are varenicline (Champix) used for smoking cessation, aripiprazole (Abilify) used for the treatment of schizophrenia, buprenorphine-naloxone (Suboxone) used as substitution treatment for opiod drug dependence as well as rimonabant (Acomplia) used for the treatment of obesity. Varenicline, buprenorphine-naloxone and rimonabant have been granted marketing authorisations within the past two years, although buprenorphine-naloxone has been available before that trough named patient use. Escitalopram (Cipralex, marketed since 2003) is also a newcomer on the list of most frequently reported medicinal substances. Well-known medicinal substances nitrofurantoin (Nitrofur-C) is back on the list with it's pulmonary ADRs. Infliximab, which is used for the treatment of e.g. rheumatoid arthritis, inflammatory bowel diseases and psoriasis, is now on the second place on this list. The number of ADR reports regarding infliximab doubled during last year, while the consumption also has increased year by year. On the third place is clozapine which has been on the fifth place on the lowest during the last 10 years.

Most of the reports received concerned medicines from the ATC-classifications Nervous system (N), Antineoplastic and immunomodulating agents (L) and Cardiovascular system (C).

The reported ADRs are coded with MedDRA (Medical Dictionary for Regulatory Activities). Most of the reports included ADRs from the system organ class (SOC) General disorders and administration site conditions. It was followed by ADRs from SOCs Gastrointestinal disorders, Skin and subcutaneous tissue disorders and Nervous system disorders. Most often reported individual ADR was rash (88), followed by urticaria (74), hepatic function test abnormalities (66), allergic or anaphylactic reaction (63) and decreased white blood cell count i.e. leukopenia of various severity.

Table 1. *Criteria of serious ADR:*

- *resulted in death*
- *was life-threatening*
- *caused/prolonged hospitalisation*
- *caused disabling/incapacitating defect*
- *caused congenital anomaly/birth defect*

Safety of medicinal substances cannot be compared with one another on the basis of the number of ADR reports. There is substantial variation in the consumption of the listed medicinal substances, and ADRs are reported more often from medicinal substances that frequently used than for those less commonly used. In addition, the reporting activity can be influenced by for example media visibility of a certain drug safety issue, or by the recommendation by NAM to report especially serious ADRs, suspected interactions, unexpected ADRs or suspected ADRs of medicinal substances that have been on the market for less that two years, or if the reporter feels that the frequency of a certain ADR appears to have increased.

Contrast media

Altogether 59 reports concerning iodine-containing contrast media were received and 47 of these concerned iomeprol (Iomeron). Most of the reports were received from the same district, reflecting similar local reporting activity as was seen the previous year. The reports received most often included urticaria (24), vomiting and/or nausea (25), or other allergic symptoms like dyspnoea or swelling of mouth or throat. Anaphylactic reaction or shock was reported four times, of which two from iomeprol. No reports with fatal outcome were received.

Selective immunosuppressive agents and methotrexate

Most of the reports received from tumour necrosis factor alpha (TNF-alpha) inhibitors concerned infliximab, which has been the longest on the market in Finland from this therapy group. Most of the reports concerned anaphylaxis or allergic reaction (7), or miscellaneous symptoms related to those (11), infusion-related symptoms (10) or various infections (10). These reflect the nature of the product (monoclonal antibody), its mechanism of action and the intravenous administration route.

Etanersept (Enbrel) belongs to the similar therapy group and is a fusion protein that competitively inhibits the binding of TNF-alpha to the surface receptors of cells. It is administered as subcutaneous injections, and the indications for use include rheumatoid arthritis, psoriatic arthritis and plaque psoriasis. Altogether 16 reports from infliximab were received: injection site reactions were described in three and dermatological symptoms in five. In addition one case of lymphoma and two infections were reported, including tuberculous peritonitis and viral encephalitis.

Adalimumab (Humira) is also a monoclonal antibody that specifically binds to TNF. It is used in the treatment of for example rheumatoid arthritis, Crohn's disease and psoriasis. Altogether 12 reports of adalimumab were received, including two reports of tuberculosis.

When treating rheumatoid arthritis all the above medicinal substances are primarily used in combination with methotrexate. Altogether 12 reports concerning methotrexate were received, four of which concerned hepatic ADRs, three pulmonary disorders and one progressive multifocal leukoencephalopathy.

Antipsychotics

While clozapine was the most often reported, also reports from other antipsychotics were received: 22 reports of quetiapine (Seroquel, Ketipinor), 18 of aripiprazole and 13 of risperidone. Most of the reports concerning clozapine included leukopenia of various seriousness (24), and in addition on pericarditis were reported (3).

Aripiprazole has been on the market for the treatment of schizophrenia since 2004, and during 2007 the use of it almost doubled when compared to the previous year. Most of the reported ADRs were neurological symptoms like extrapyramidal movement disorders and tardive dyskinesia (3 altogether) as well as neuroleptic malignant syndrome (3). In addition gastrointestinal symptoms (5), various psychiatric behaviour disorders (4), one of which was suicide attempt, and leukopenias (3) were reported.

Table 2. *The medicinal substances most frequently reported in 2007.*

iomeprol	*47*
infliximab	*46*
clozapine	*38*
pregabalin	*34*
duloxetine	*30*
simvastatin	*29*
varenicline	*23*
terbinafine	*22*
quetiapine	*22*
etonogestrel-ethinylestradiol	*20*
etoricoxib	*19*
aripiprazole	*18*
levofloxacin	*16*
etanercept	*16*
levonorgestrel (IUD)	*14*
mirtazapine	*14*
risperidone	*13*
fluvastatin	*12*
drosperidone-ethinylestradiol	*12*
nitrofurantoin	*12*
capecitabine	*12*
bevacizumab	*12*
adalimumab	*12*
methotrexate	*12*
buprenorphine-naloxone	*11*
rimonabant	*10*
rituximab	*10*
escitalopram	*10*
venlafaxine	*10*

Neuroleptic malignant syndrome was reported twice also related with the use of quetiapine. In addition tardive dyskinesia (2) and other neurological symptoms (7) were reported for quetiapine. The most often reported ADRs for risperidone were also various neurological movement disorders (8) and neuroleptic malignant syndrome (2).

Antidepressants

Duloxetine (Cymbalta) has been on the market since 2005, and most of the ADRs reported were neurological (16) and psychiatric (14), including e.g. dizziness and balance disorders (6), as well as

suicidal thoughts or suicide attempt (3). Also various gastrointestinal ADRs were described in 10 reports. In addition to depression other indications for duloxetine use are the treatment of peripheral diabetic neuropatic pain and female stress urinary incontinence.

Altogether 14 reports were received on mirtazapine, including e.g neurological symptoms (11) like restless legs and muscle twitching, as well as dermatological symptoms (4).

Ten reports were received for both venlafaxine (Efexor depot) and escitalopram. In the case of escitalopram, 3 reports concerned suicide or suicide attempt. Suicidal thoughts were reported in one case related with use of venlafaxine. In addition, various cardiovascular ADRs were reported, including palpitations, tachycardia or high or low blood pressure.

The Committee of Human Medicinal Products (CHMP) of the EMEA has performed a class review of antidepressants and the risk of suicide among young adult patients. The summaries of product characteristics (SPC) and packet leaflets (PL) of antidepressants are further specified on this issuer during this spring.

Pregabalin

GABA analogue pregabalin (Lyrica) was introduced to the Finnish market in 2004 for the treatment of neuropatic pain, epilepsy and later on for generalised anxiety disorders. It's use has increased almost 50 % every year. In great majority of the 34 reports received last year the indication for use was (neuropatic) pain. As during the years before, majority of the reported ADRs were psychiatric and neurological symptoms. In addition various general symptoms were reported, including feeling hot and oedema (5 of each).

Statins

The reimbursement practice of statins changed in Finland during the last part of year 2006, and the consumption of simvastatin increased over 50 % during 2007 when compared to the previous year. Also the number of ADRs reported for simvastatin increased. The reported ADRs were mostly known and affected the muscles: rhabdomyolysis (4), myalgia and muscle cramps or increased creatine kinase (CK) levels (altogether 8). In addition various dermatological ADRs (5) and hepatic failure (2) were reported.

The consumption of fluvastatin increased by a quarter compared to the previous year. For the other statins the use decreased. The reported ADRs were mostly similar to the above: increased CK and hepatic enzyme levels.

Medicines used in addictive disorders

Varenicline, which is used for smoking cessation, was granted marketing authorisation trough the centralised procedure in September 2006, and thus most of the usage experience has cumulated during last year. The CHMP also assessed the safety of varenicline last year, especially regarding psychiatric ADRs and suicidal thoughts, and the SPCs and PLs will be completed during this spring.

The ADRs reported to NAM on varenicline most often concerned nausea and other gastrointestinal symptoms (10), dermatological symptoms (8), muscle cramps or myalgia (5) and various general symptoms like oedema or tiredness (4 of each).

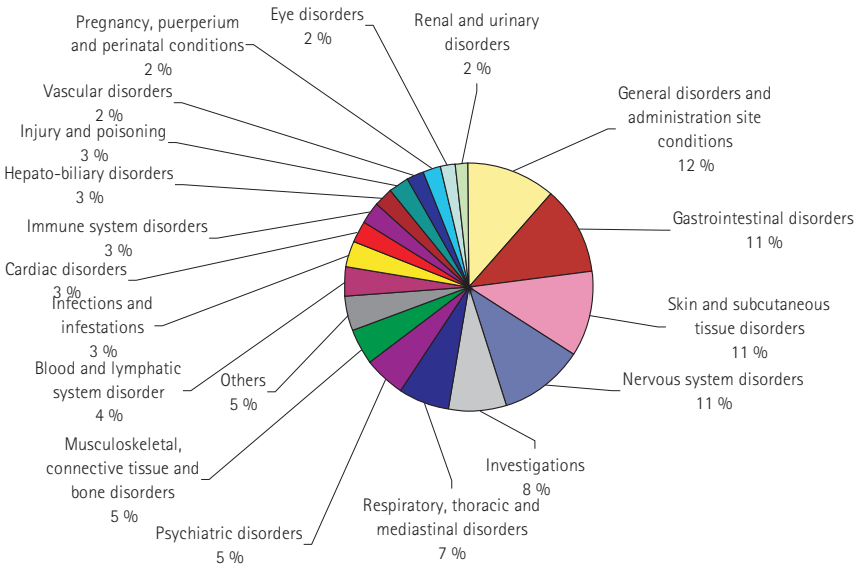

Fig. Reported adverse drug reactions (n=2 568) according to SOCs in 2007.

Altogether 8 psychiatric ADRs were reported: 2 of them concerned mania or psychosis, 3 sleeping difficulties and the rest isolated psychiatric symptoms. There were no reports of suicidal thoughts during year 2007; some have been received during 2008.

Buprenorphine-naloxone is a combination product; buprenorphine binds slowly and reversibly to the myy-opioid receptors in the brain. Naloxone is an antagonist of the same receptor type, and when given orally to patients experiencing withdrawal symptoms it has minimal pharmacological effect, but when administered intravenously it causes notable antagonist effect and withdrawal symptoms, thus preventing intravenous abuse.

The consumption of buprenorphine-naloxone has increased evenly, without any remarkable peak in 2007, at the end of which Subutex, which contains only buprenorphine, remained available only trough named patient use for pregnant patients.

All the 11 reports received arrived during the same week and concerned various symptoms of teeth, including tooth pain, tooth loss and erosion. In all the cases the original report was completed by the patient himself at the presence of a nurse, who then had submitted the reports to the marketing authorisation holder, after having herself seen the conditions of the patients' teeth. Further information was requested from the treating physician(s), but the previous condition of the patients' teeth was not familiar to the physician. No clear causal relationship between the symptoms and the treatment was suspected at this point.

Coxibs

Rofecoxib was withdrawn from the market on 2004 due to serious thrombotic cardiovascular events. This action was followed by a class review of the other coxibs, and in 2005 the marketing authorisation (MA) of valdecoxib was suspended due to serious dermatological ADRs. The latest recommendation from the CHMP was on 2007 to withdraw the marketing authorisations of lumiracoxib due to serious hepatic ADRs.

There are two orally administered coxibs still in use in Finland: celecoxib (Celebra) which was granted the MA in 2000 and etoricoxib (Arcoxia) since 2002. The consumption of celecoxib has decreased slightly year by year, whereas that of etoricoxib has increased. When compared to the defined daily dose (DDD)-estimates the use of etoricoxib was on the same level as that of diclofenac and ketoprofen, regardless of the news on coxibs and the more limited indication.

ADRs related to etoricoxib were reported in 19 reports. Most of them concerned gastrointestinal or dermatological symptoms (5 of each). Cardiovascular or hepatic ADRS were reported twice. Dermatological symptoms in connection to celecoxib use were reported twice.

Contraceptives

Nuvaring contraceptive vaginal ring (etonorgestrel-ethinylestradiol) was reported 20 times, 15 of which concerned unintended pregnancy, one extra uterine pregnancy, one deep venous thrombosis and one pulmonary embolism. All the 14 reports of levonorgestrel concerned Mirena, a hormonal IUD. Unintended or extra uterine pregnancy was described in four reports. The ADRs described in the rest of the reports were various. In addition, 12 reports of drospirenone-ethinylestradiol (11 Yasmin, 1 Yasminelle) were received. Unintended pregnancy was reported in four of these, cerebral infarction in two and pulmonary embolism in one of these reports.

Antineoplastic agents

Vascular endothelial growth factor (VEGF) inhibitor bevacizumab was reported 14 times and 5-fluorouracil precursor capecitabine 13 times. The patients described in these reports were often in poor condition to start with due to the background disease. A few neutropenic infections and cardiovascular symptoms were reported in connection to capecitabine. Various ADRs were reported for bevacizumab, including e.g. intestinal perforation, cerebral infarction, hemiparesis and paraparesis.

Rimonabant

Rimonabant is used for the treatment of obesity and affects the endocannabinoid system. It was granted marketing authorisation in 2006. Last year 10 ADR reports were received, including various events. Depression or apathy was described in three reports. During summer 2007 CHMP concluded that the warning regarding depression in the SPC was to be changed to become a contraindication of treatment.

Conclusion

NAM wishes to thank all health care professional for reporting ADRs. Spontaneous reporting is important because especially rare ADRs can be detected only after wider use and when different patient populations are treated. A suspected ADR is worth reporting especially if it is serious, unexpected or the suspected drug is new and has been on the market less than two years.