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

The many dimensions of narcotics control in Finland

What do the analgetic morphine, the sedative diazepam, and acetone, used as an industrial solvent, have in common? What is the common denominator linking pharmaceutical companies, pharmaceutical wholesalers and pharmacies, the chemical industry, and the municipal waterworks? The answer: Although these substances and groups are very different, they all fall under NAM's scope of responsibility in the field of narcotics control.

The new Act on Narcotics (373/2008) will enter into force on 1st September 2008. Narcotics control will be improved thanks to the new procedures that are to be introduced with regard to permits and notices, with increased co-operation between authorities. The responsibilities and duties of those parties involved in dealing with narcotics will be emphasised more precisely in the applicable legal provisions.

International narcotics control is based on the United Nations Conventions; the principle governing these is to ensure the availability of controlled substances for medicinal use and scientific research, while preventing abuse of the substances. The Single Conventions on Narcotic Drugs from 1961 and Psychotropic Substances from 1971 are still the key instruments of narcotics legislation. The new Act will not affect the principles of Finland's national narcotics policy.

The term 'narcotic substance' gives rise to powerful associations which frequently cause confusion in patients. For its definition of a narcotic substance, national legislation continues to rely on the substances listed in the international conventions. Opioids, for example, and the majority of medicines whose main effect is a CNS effect, fall within the scope of the conventions and are therefore legally narcotic substances. Justified medicinal use of the substances in the treatment of patients should be clearly distinguished from abuse, which leads to dependency.

Control of the precursors used in the manufacture of narcotic substances is also the responsibility of the National Agency for Medicines. The precursors regulated include some substances which are also used as medicines, and certain commonly-used, high-volume industrial chemicals, which are needed for the manufacture of narcotics. Water purification processes may involve the use of potassium permanganate, the use of which, if it exceeds a certain threshold value, requires user registration with NAM. The same chemical is also used in the manufacture of cocaine. Narcotics and narcotics control thus have some unexpected dimensions.

Areas of concern in the enactment of the law included falsification of prescriptions for medicines which are classified as narcotics, and the risk of these medicines becoming the object of abuse. Special issues raised included new substances which are imported and used for purposes of intoxication, but which are not actually narcotics. What quick action can be taken here? Classifying them nationally as narcotics is not a possibility, whereas having the substance regulated under international control is a long process. There are still a number of issues awaiting to be resolved.

The long process of drafting legislation has reached its end, and the process of practical implementation of the new regulation procedures has started. This provides an opportunity to re-examine the present procedures. New duties of supervision at NAM have furthermore required consolidation of resources. NAM is a key authority in the regulation of the legalised use of narcotic substances and their precursors.

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Problems of drug treatment in the elderly in accident and emergency departments

As the population ages, increase in the number of diseases associated with the usual ageing process is an obvious reason for the common sight of elderly patients (over 75–80 years of age) in accident and emergency departments. The elderly admitted to these departments typically have multiple diseases and use several drugs. This paper discusses drug treatment of the elderly as a cause of hospitalisation, and it also deals with how drug treatment should be taken into account when planning treatment.

Drug treatment and reasons for admission to accident and emergency departments

Drug treatment can lead to hospitalisation in several ways, and this, along with associated adverse drug reactions has often been considered a significant cause of hospitalisation of the elderly. The combination of diseases and drug treatment makes assessment difficult, however. With regard to the elderly in particular, it is often difficult to unravel whether the cause is medication or a disease. *Confounding by indication* should be taken into account when causal relationships are examined. Indicative figures have been received from studies in recent years. An extensive British study (covering nearly 19,000 emergency attendances), about 6.5% of the causes of hospitalisation were the result of adverse drug reactions (1). The average age of these patients was 76 years. This correlated well with a study carried out in 1996, consisting of a review of elderly Finnish patients: adverse drug reactions were the cause of hospitalisation in 6% of them (2). According to an American study, every year 4% of elderly drug users experience a severe adverse drug reaction (3). Of all adverse drug reactions, less than 1% led to death (3). The outcome was lethal in 2% of the patients who had adverse reactions requiring hospitalisation (1).

A recent Swedish review consisted of a one-month analysis of the reasons, associated with drug treatment for admission to a university hospital internal medicine emergency department (4). The total number of patients with an average age of 68 years was 1,176, 39% of whom were hospitalised (n=457). Of the patients, 135 (12% of the total number, 30% of those hospitalised) were considered to have problems with drug treatment which either directly or indirectly were the cause of them requiring hospitalisation. Of these patients, 73% were assessed as having experienced a drug-induced symptom, the drug treatment was inadequate or otherwise unsuccessful in 30%, toxicity was the cause for hospitalisation in 5%, and drug abuse in 11% of the patients, and 48% of them were thought to have experienced a clinically significant interaction. The figures of adverse drug reactions in the Swedish study are quite high, but the study was carried out in a university hospital (Karolinska Hospital, Stockholm) where the patients have severe multiple diseases (cardiology, haematology and cancer patients) and are consequently on multiple drugs (average of 9 drugs); a third of the patients suffered from renal failure.

Table 1. *Categorisation of adverse reactions associated with drug treatment*

Intentional overdose

Involuntary adverse reactions

- *allergic reactions (transmitted via the immune system)*
- *actual adverse reactions (pharmacological or idiosyncratic reactions associated with usual doses)*
- *involuntary overdose*
- *secondary reactions (e.g. a fall associated with hypotension)*
- *interaction with another drug or disease*

Table 2. *Key inducers of severe drug reactions (not in order of importance)*

- *Warfarin*
- *Acetylsalicylic acid*
- *Anti-inflammatory analgesics*
- *Diuretics*
- *ACE inhibitors*
- *Beta-blockers*
- *Insulin and oral antidiabetic agents*
- *Antimicrobials*
- *Drugs with a narrow therapeutic range (e.g. lithium)*

Adverse reactions associated with drug treatment can be categorised as shown in Table 1.

All types of adverse reactions, including intentional overdose, may occur in the elderly, and particularly in the case of an elderly person with memory loss, an involuntary overdose should also be considered. An adverse reaction associated with the drug or its secondary reaction is often a *contemplated risk* which is taken when treatment for a disease is necessary. Well-known examples of these include the risk of haemorrhage with the use of warfarin and the side-effects associated with antibiotic and corticosteroid therapy. In general, the majority of the significant adverse drug reactions experienced by the elderly are associated with well-known and widely used drugs such as anticoagulants, anti-inflammatory analgesics and antidiabetic agents, whereas surprisingly few are associated with drugs that can be called inappropriate (5) (Table 2).

The interrelation between the medication of 450 elderly patients and their hospitalisation was analysed in a Finnish study published in 1996 (2). The most significant causes were extrapyramidal symptoms caused by antipsychotics, haemorrhage caused by warfarin and anti-inflammatory analgesics, and diarrhoea caused by antibiotics.

In a British study, typical severe adverse reactions included intestinal haemorrhage caused by acetylsalicylic acid, other anti-inflammatory analgesics and warfarin; hypotension or renal failure caused by diuretics or ACE inhibitors; antidepressant induced confusion, hypotension, constipation, intestinal haemorrhage or hyponatraemia; and beta-blocker induced bradycardia, hypotension and chronic obstructive pulmonary disease (1).

In an American study (3, 5), cardiovascular drugs, antibiotics, diuretics and anti-inflammatory analgesics were also considered to be the most common causes of adverse reactions.

An important message to come out of the studies has also been the fact that a very high proportion of the adverse drug reactions suffered by the elderly are preventable. It is estimated that as many as 40% to 70% of the reactions are avoidable in ideal circumstances and by correct adjustment of the drug dose, for example (1–4). On the other hand, even though antibiotics generally cause adverse reactions, only a small proportion of them could be prevented (3). In severe adverse reactions the possibility of prevention is generally estimated to be higher than in milder reactions. This promotes improved identification of adverse drug reactions and their causes.

Multi-drug medication may cause interactions. A British study showed the proportion of interactions to be 16.6% of adverse drug reactions (1), but in patients with multiple diseases and on multiple drug therapies at a Swedish university hospital, it was estimated that every second patient experienced a clinically significant interaction (4). Nevertheless, it is generally estimated that interactions are theoretically are very common, but only a small proportion are clinically significant (6). A Canadian study comprising patients aged over 65 with osteoarthritis, showed the ratio of interactions of clinically significant drug interactions and all possible interactions to be 1:6 (7), i.e. about 16% of interactions were significant. The important drugs to bear in mind in respect of interactions include the well-known warfarin, acetylsalicylic acid and diuretics. Nevertheless, a clinician treating elderly patients should be aware of these and should avoid possibly hazardous interactions. Nowadays significant interactions can be identified, even at the bedside, with the help of the SFINX database, for example (*www.terveysportti.fi*). The important drugs to bear in mind are listed in Table 3.

Table 3. *Possibility of an interaction to be borne in mind when elderly people are on any of the following drug therapies*

- *Warfarin*
- *Acetylsalicylic acid*
- *Diuretics*
- *Amitriptyline*
- *Doxepin*
- *Fluoxetine*
- *Levomepromazine*
- *Perphenazine*
- *Phenytoin*
- *Carbamazepine*
- *Alprazolam*
- *Diazepam*
- *Midazolam*
- *Triazolam*
- *Diltiazem*
- *Verapamil*
- *Omeprazole*
- *Antifungals*

Typical and unexpected interactions of drugs metabolised via the liver, and which should be accounted for in the treatment of the elderly, are considered in a recent Finnish review (8). Several drugs causing significant interactions can in fact be considered inappropriate for the elderly from the start, because there are safer alternatives.

Table 4. *Specific symptoms of elderly patients in emergency departments which may influence drug therapy*

- *Delirium – drugs with a CNS effect, anticholinergics*
- *Cognitive impairment – drugs with CNS effect, anticholinergics*
- *Frailty syndrome – impairment of the body's reserves, drug response*
- *Tendency to fall over - drugs with a CNS effect, antihypertensives*
- *Impaired renal function – drug response, electrolyte disturbances*
- *Orthostatic hypotension - antihypertensive medication*

Problems associated with treatment and specific symptoms of the elderly while receiving drug treatment

Even though drug treatment of the elderly in emergency departments often takes place following principles similar to those applied in younger patients, elderly patients may have special characteristics which should be considered when planning their drug treatment (Table 4).

Renal function is often impaired – exposing the patient to e.g. electrolyte disturbances and adverse drug reactions – and the creatinine level alone does not reveal the whole truth about the condition of the patient's kidneys. The elderly patient may suffer from orthostatic hypotension, and measurement of blood pressure as well in the upright position is important when management with antihypertensives and antihypotensives is planned. Delirium, tendency to fall over, cognitive impairment (dementia) and frailty syndrome, especially common in those over 80, also have an effect on other diseases and associated treatment. It is recommended that these special problems be identified, but an elderly person's dementia must not lead to unnecessarily negative attitudes, for example. Infections and cardiac problems in dementia patients must also be treated. Frailty syndrome, dementia and delirium are associated with reduced capacity of the body's reserves, in which case the drug response may be unexpectedly strong. Anticholinergics in particular should be avoided and, should their use be necessary, the response should be carefully monitored, especially in patients with dementia and delirium (9). Since the elderly are usually on several drug therapies, a thorough review of an updated list of drugs (not forgetting any herbal and natural remedies which the patient does not necessarily mention) is important both in the assessment of possible hospitalisation and planning of future management. Problems often occur with the availability of an updated list of drugs, however. Development including the common use of IT systems is required, as well as sharing of responsibility with regard to who is registering what and into where. Good readability of lists of drugs is also very important.

Problems with medication following attendance at the emergency department

Medication introduced in emergency care also influences the patient's future condition, as discovered among emergency unit patients over 65 years of age in an American hospital for veterans (10). Of the patients, 45% (942) had received one or more new drugs during an attendance. A third of the patients experienced potential problems associated with the newly introduced drug: inappropriate medication, a drug interaction or a drug–disease interaction. A third of the veterans were rehospitalised and the outcome was fatal for 2% during the follow-up period. Problems associated with medication increased these risks by 32%. In an effort to reduce the number of future emergency attendances, improved monitoring of drug treatment should be considered.

Conclusion

An adverse drug reaction may be a significant reason why an elderly patient is admitted to an emergency department. Adverse drug reactions may often, however, be well-known adverse reactions of a drug which is essential. The most common ones include warfarin, acetylsalicylic acid, anti-inflammatory analgesics, diuretics, ACE inhibitors, beta-blockers and insulin. A disease in an elderly patient may, on the other hand, significantly reduce the drug response.

While the elderly patient is in the emergency department, the following should be considered

- check what medicines and herbal remedies were used, including the part they played in the fact that the patient was hospitalised.
- check whether the patient suffers from a frailty syndrome, dementia, delirium, renal failure (not necessarily shown by the creatinine level) or orthostatic hypotension, and adjust the drug treatment accordingly. Since a significant proportion of drug adverse reactions are preventable, special attention should be paid to the drug treatments introduced in the emergency department including their efficacy, and to monitoring their effects.

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Somatic follow-up and drug treatment in schizophrenia patients

Schizophrenia, the most difficult type of psychosis, is a multiform psychiatric disease affecting about one percent of the adult population. Schizophrenia has often been considered a chronic disorder, but prognosis can be improved by early identification of the disease and early introduction of treatment. Key issues in management include an antipsychotic medication aimed at using the smallest effective dose and minimising adverse reactions.

Management of schizophrenia is based on a long-term relationship and an individual management plan which is regularly reviewed and which takes into consideration the needs of the patient and of those nearest to him/her. Key issues in management include an antipsychotic medication aimed at using the smallest effective dose and minimising adverse reactions; various forms of individual psychosocial treatment, education of the whole family about the disease, and forms of social rehabilitation. In long-term management it is important to support the patients adherence to their treatment; equally important are flexible services in crisis situations and prevention of new episodes of illness. (1).

Used regularly, antipsychotics alleviate symptoms of the acute stage and prevent recurrence of psychosis. Antipsychotics are often used for a long time over years and decades, and long-term tolerability in particular is consequently important. As conventional antipsychotics are not effective in all patients and their use is associated with a large number of neurological adverse effects, new drugs have been developed with a broader effect on psychotic symptoms and a better level of tolerance. It has nevertheless been found in recent years that antipsychotics can have metabolic and cardiovascular effects. Long-term weight increase is the biggest risk factor for adult type diabetes, and metabolic syndrome associated with being overweight also includes other significant cardiovascular risk factors. Identifying changes in metabolism and weight linked to the use of antipsychotics is important and helps to improve the benefit/adverse effect ratio. Selecting the correct antipsychotic, avoiding multiple medications, giving nutritional advice, measuring weight regularly and participating in a diet program as necessary can decrease these adverse effects. Regular monitoring in line with recent recommendations can improve the prognosis for this patient group (2).

Sugar metabolism disorders

Impaired control of diabetes, as well as new incidences of diabetes have been described in the use of anti-psychotics; in particular, if the patient was overweight at the outset of treatment or the weight was increased significantly at the start of the treatment. Incidences of diabetes have been described both with conventional antipsychotics and with second generation drugs. The prevalence of diabetes or impaired tolerance of sugar in schizophrenic patients is difficult to assess, but figures in the range of 2.7%–36.6% have been suggested. In small trials the risk of diabetes is estimated to be

Follow-up of symptoms in patients using antipsychotics

	Medication initiation	*4 weeks after initiation*	*8 weeks after initiation*	*12 weeks after initiation*	*Every third month*	*Yearly*	*Every fifth years*
Family background (diabetes, lipid metabolism dysunction, sudden death)	x					x	
Weight (weight index)	x	x	x	x	x		
Waistline	x					x	
Blood pressure	x			x		x	
Fasting glucose	x			x		x	
Lipids (total cholesterol, HDL- and LDL-cholesterol, triglycerides)	x			x			x

about two to four times higher in comparison with the normal population. According to a recent extensive study, the development of diabetes is more common in patients on second generation antipsychotics, especially in patients under 40 years of age (3).

Changes in fat metabolism

The exact cause of lipid changes associated with antipsychotic therapy is unclear, but lipid changes may be linked to the weight gain associated with the use of these drugs. Accumulating fat around the middle of the body increases the presences of free fatty acids in the liver, accelerates liver triglyceride synthesis and VLDL lipoprotein secretion. The increased concentration of free fatty acids may also compete with the absorption of glucose, especially in muscle tissues, and may lead to impaired sugar tolerance and type 2 diabetes. Among the conventional anti-psychotics, soon after their introduction on to the market phenothiazines (e.g. chlorpromazine) were found to increase the serum cholesterol and particularly triglyceride concentrations; with butyrophenones, such as haloperidol the corresponding effects were somewhat smaller. Among the second generation antipsychotics clozapine therapy has been found to increase serum cholesterol and triglyceride concentrations, and effect of olanzapine in increasing cholesterol concentration has been found to be associated with weight gain (4, 5).

Weight gain, metabolic changes and treatment regimes

Management of a schizophrenic patient includes a somatic examination at the initial stage of the treatment and regularly thereafter (at about 6–12 month intervals), the aim of which is to identify any other somatic diseases and any adverse reactions in the schizophrenic patient, which are associated with the treatment (Table), (6). The intervals shown in the table, at which the laboratory tests are repeated, are given as a guideline, and depending on a clinical assessment, there may even be a need for more frequent tests. Monitoring of weight, or the weight index, monthly or at appointments, is also recommended, including ECG monitoring (before the introduction of drug treatment and once the dosage is stabilised) especially in patients on high doses of antipsychotics. According to international studies, every other schizophrenic patient has a problem with intoxicants, but the proportion of intoxicant abusers was smaller among Finnish patients. To identify any problems with intoxicants it is recommended that in addition to the patient, the patient's nearest relatives be interviewed and that laboratory assays be used to supplement the somatic examination.

Correct choice of antipsychotic, avoidance of polypharmacy, nutritional guidelines, regular monitoring of weight, and participation in a diet programme as necessary, may reduce the adverse reactions caused by weight gain and changes in metabolism. Nutritional guidelines are aimed at reducing the amount of harmful fat contained in the diet, and exercise is aimed at reducing the calorie consumption, although only modest results have been achieved with the latter. Weight monitoring is of particular importance during the first weeks and months of treatment. Since weight gain and metabolic changes may be associated with the antipsychotic dose given, use of the smallest effective dose in

the treatment of the psychosis is also justified from this point of view (1). Replacing the antipsychotic with another one may also be beneficial, because diabetes may disappear in the changeover to another drug. Recommendations for a replacement do, however, require further comparisons between different molecules.

According to present knowledge, the importance of drug therapy aimed at weight control is minor, because many of the drugs used in weight control have an effect on the dopamine and serotonin receptors in the same way that antipsychotics do. Consequently, for example, the use of sibutramine, originally developed as a antidepressant with an inhibitive effect both on noradrenalin and serotonin re-uptake, has been considered as being contraindicated in patients suffering from a psychosis, because of the risk of adverse effects linked to its monoamine re-uptake inhibition such as exacerbation of psychosis and serotonin syndrome. Increased prolactin secretion caused by dopamine receptor blockade can increase androgen production, and the change in the oestrogen/androgen ratio may increase appetite and fatty accumulation. In cases followed up over a longer period, with an opposite effect, the dopamine agonist amantadine has been found to stop the weight gain associated with the use of olanzapine, for example, and to decrease patients' weight. The use of amantadine is nevertheless associated with the risk of exacerbation of psychotic symptoms. Orlistat, with its effect on fat absorption, is a drug with a proven efficacy in weight reduction, but there is insufficient evidence available on its use in cases of weight gain associated with antipsychotic use. In addition to a diet, treatment of fat metabolism disorders in psychotic patients with, for example, statins, is a possibility, but further studies are still needed in order to provide proper treatment recommendations. Adverse cardiovascular events caused by a fat metabolism disorder may be reduced by using small doses of acetylsalicylic acid.

The clinical significance of metabolic disorders caused by antipsychotics

Patients have a very negative attitude towards antipsychotic therapy if, despite the medication, significant positive hallucination symptoms occur and the therapy causes tiredness. Consequently, particularly in the treatment of schizophrenia and the other most severe psychoses, more effective drug therapies with improved tolerability are needed. The above-mentioned adverse reactions, reflected in weight gain and adverse metabolic reactions do not eliminate the positive effects of antipsychotic therapy. In addition to more effective alleviation of psychotic symptoms, benefits of the second generation products also include decreased adverse neurological symptoms and a beneficial effect on the patient's cognition, symptoms of depression and suicide mortality. The choice of drug should still be based on assessment of the patient's entire situation and not only of isolated adverse reactions. New understanding is nevertheless needed about the importance of the above-mentioned advantages and disadvantages in long-term treatment.

Efforts should be made to reduce the adverse reactions caused by medication; for example, by appropriate monitoring of the effects on weight and metabolism in patients on regular antipsychotic therapy, as part of the patient's total clinical monitoring. Simultaneous efforts can be made to influence any other health risk factors (smoking, hypertension, diabetes) as part of the treatment arrangements. In order for the outcome of treatment and any associated adverse reactions to be monitored, patient records should contain adequate information to give detailed account of how the treatment was carried out.

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Surveillance of tissue establishments in Finland

2007 was a busy year for tissue establishments and the National Agency for Medicines (NAM), which is responsible for tissue regulation, because three EU Directives regulating the services of the establishments were adopted nationally within just a short time frame. According to the new regulations, tissue establishments need to be licensed. The quality and safety of human tissues and cells are safeguarded through the licensing of tissue services, the appointment of the responsible individuals, trained and experienced personnel, appropriate premises, equipment and materials, and the documentation relating to the services.

An amendment to the Human Tissue Act (101/2001) regarding the medical use of human organs and tissues entered into force on 1.6.2007. The reformed Act implemented the European Parliament and Council Tissue Directive 2004/23/EC at national level. According to the reformed Tissue Act, all tissue establishments operating in Finland needed to apply to NAM for a licence for their operation by 1.9.2007 at the latest. Those tissue establishments which submitted their application for a licence by the due date then had the right to continue their operations until the licensing issue was resolved.

The Decree of the Ministry of Social Affairs and Health regarding medical use of human tissues and cells (1302/2007) and NAM's Administrative Regulation regarding technical requirements for the operation of tissue establishments (3/2007) came into force on 28.12.2007. The Decree and the Administrative Regulation were followed by the national implementation of the Commission Directives 2006/17/EC and 2006/86/EC.

The regulation of tissue establishments represented a new area of responsibility for NAM, consisting, for example, in establishing regulatory and licensing procedures and providing guidelines and advice to the establishments. As the regulations focussed on the quality and safety of human tissues and cells, in its new area of responsibility NAM was able to make full use of its experience in the quality and safety regulation of drugs and blood products and the regulation of medical devices.

When the amendment to the Tissue Act came into force, NAM organised a meeting for the operators of tissue establishments, where the new tissue safety legislation and associated requirements were discussed. A total of 43 representatives from various tissue establishments around Finland attended the meeting. During a lively discussion it was argued that adopting the quality and safety requirements in such a way as to suit various, very different types of tissues and cells could pose a particular challenge. Further concern was expressed as

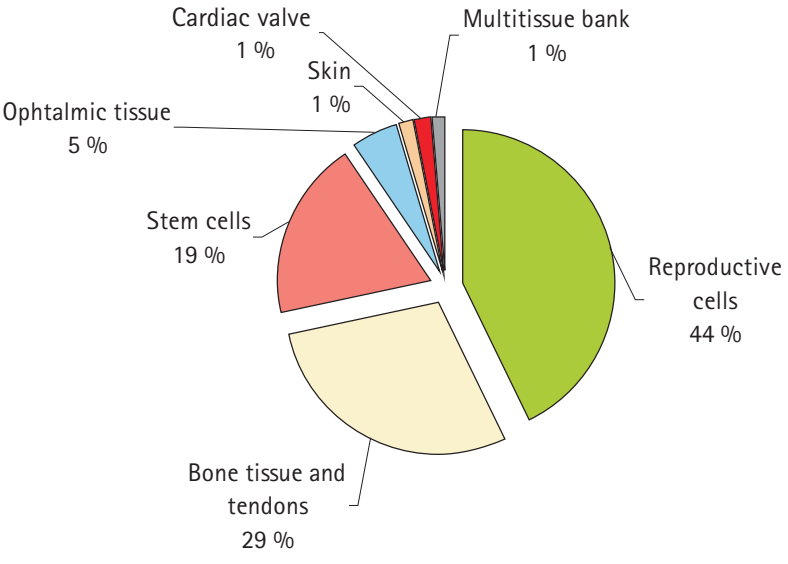

Fig. 1. Applications.

to whether the information regarding the applicable requirements would reach all of the operators. In addition to the importance of NAM communicating with the operators on the responsibility of the operators themselves to follow and comply with the legislation.

Information reagrding regulation of tissue establishments was added to NAM's website. To help licence applicants and to improve the licensing process, a licence application form was included on the website. The form also includes details about the reports required for the licence application as set out in the Decree (773/2007) that came into force on 20.7.2007. There are links to current rules and regulations governing tissue establishments. During the summer and autumn of 2007, regulatory officers responsible for the regulation of tissue establishments responded to numerous requests for information relating to licences and the application process.

At the turn of the year 2007/2008, when all three directives were nationally implemented, NAM provided all licence applicants with an information pack about the national legal provisions. Operators were also reminded of the national reviews with regard to emergency situations affecting tissue and cell imports, and communication procedures regarding tissue vigilance.

Applications

Over 600 licence applications from about 70 establishments, were submitted to NAM by the due date. The majority of the applications were from fertility treatment units using gametes, bone banks, and units conducting stem cell therapy (blood and bone marrow stem cells). Applications were also submitted for licences for the handling and storage of eye cornea and sclera, amnia, cardiac valves and skin (Fig. 1).

Preliminary inspections

NAM inspects all of the operators and establishments applying for an accredited tissue establishment licence. By June 2008, regulatory officers responsible for tissue establishments will have inspected a total of about 58 units, i.e. 80% of all applicants. The purpose of the preliminary inspections was to make a practical assessment of the prerequisites for applicants to carry on their business as tissue establishments. Particular efforts were made to find staff involved in the practical work of these establishments who could also participate in NAM's inspection duties. In addition to their regulatory component, inspections have also typically provided opportunities for delivering guidelines and advice.

Inspections start with an introductory discussion, during which the inspectors elaborate on tissue regulation and associated legal stipulations, while the operators describe the general features of their own business. This is followed by a review of the establishment's compliance with all important quality and safety requirements.

The inspection ends with a final discussion, during which the observations made by the inspectors and any defects noted are reviewed together with the operator, following which the subsequent stages of the licensing process are discussed. An inspection protocol is kept, in which observations made during the inspection and any defects noted are duly recorded. The operator is supplied with a copy of the protocol after the inspection. At the same time, NAM will request a report and schedule of the remedial actions that are to be taken to rectify the defects. The licence will be prepared at NAM based on the application documents, preliminary inspection, and any additional reports submitted.

In the assessment of each tissue establishments' and its operations' compliance with regulations, particular attention is given to the following issues

- Designating a responsible person and ascertaining that he/she is appropriately qualified
- Introduction to duties, formal qualification and further training of staff
- Quality assurance system
- Auditing of the business and its quality assurance system
- Processing and assessment of any defects
- Tissue safety; processing of and reporting on any serious adverse reactions associated with tissue and cell quality and safety, and any serious adverse events
- Tissue and cell procurement procedures; donor recruitment, consent, assessment and infection testing
- Handling, preservation and storage of tissues and cells
- Release into use and distribution of tissues and cells
- Premises; in particular the premises for handling and storing tissues and cells including monitoring of their condition
- Ensuring the availability and faultless operation of all essential equipment
- Essential materials, with batch monitoring
- Full traceability of data

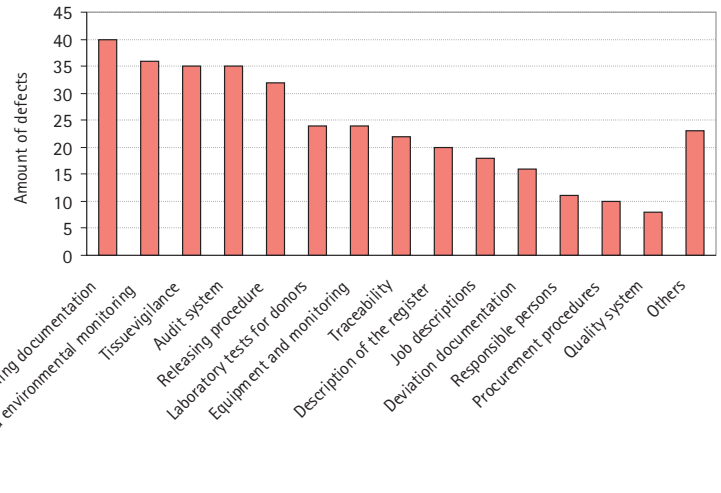

Fig. 2.

During the inspections of the 58 establishments, a total of 357 defects were recorded, 23 (6.4%) of which were assessed as critical or serious. The critical defects were associated with inaccuracies in the mandatory infection testing of tissue or cell donors. Serious defects related typically to establishments' premises which did not, in all their parts, fulfil the requirements applicable to tissue handling facilities.

The majority of the defects identified related to quality systems and inadequate documentation of operations. The range of defects found can be seen in Fig. 2.

Licences

So far, NAM has issued 21 licences for tissue establishments, and one emergency licence for import. Units inspected in the spring have actively submitted additional reports which were necessary for completion of the licence, and new licences are currently being prepared. A list of accredited tissue establishments is published by NAM. The list is available on the NAM website. Licensed tissue establishments are inspected at two-yearly intervals, in accordance with regulations.

Concerning fertility treatment services, tissue establishments which handle gemetes also need a licence from the National Board of Medicolegal Affairs, in accordance with the legislation governing fertility treatment. The licensing procedures of this Board and NAM have in part proceeded in parallel, with active collaboration between the authorities.

Tissue vigilance

Any situations that could jeopardise the quality and safety of tissues and cells should be assessed by the individual tissue establishment, with the establishment itself planning and taking remedial action. Serious adverse reactions and serious adverse events should be reported to NAM. In 2007, ten reports relating to serious hazardous situations were issued, concerning defects identified in the storage and distribution procedures for tissues and cells, and microbial contamination of transplants.

Projects in the immediate future

The European coding system that is currently under development will pose a challenge both to tissue establishments and to the regulatory authorities. Its aim is to give each donated product an individual European code, by which the donor and the transplant can be reliably identified and traced.

The Commission has been active in initiating projects to aid the setting up and development of quality systems, including harmonising the way in which they are monitored.

Tissue establishments operated in Finland before the implementation of the directives, and continue to do so today. It is hoped that the new common requirements will help to further clarify and harmonise practice at tissue establishments, and increase confidence both in Finland and abroad in the quality and safety of donated tissues and cells.

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Counterfeit medicines containing wrong active pharmaceutical ingredients

The amount of counterfeit medicines increase rapidly throughout the world. As well international organizations (1, 2) as national authorities (3, 4) work actively to counteract traffic of counterfeit medicines. Since 2006 the seizures of counterfeit medicines done buy the customs at the EU's external border have increased by 51% (5). The number of medicines and diverse counterfeit medicines seized by the Finnish Customs has also increased year after year (6). In Finland counterfeit medicines have, nevertheless, not reached the legitimate supply chain.

Although it is in most cases illegal, Finns frequently order potency promoters and doping substances through international websites. Samples confiscated at the Customs Post Office or seized from travelers at the Finnish borders are analyzed by the Finnish Customs Laboratory. For an eventual crime investigation, it is sufficient to identify any active pharmaceutical ingredient (API) in the sample; thus the focus is on qualitative analyses. Counterfeit medicines containing wrong APIs constitute, however, a serious safety concern and are therefore of special interest for the authorities supervising medicines. The laboratory of the National Agency for Medicines (NAM) has examined samples confiscated by the Finnish Customs by using qualitative and quantitative methods. This article presents five examples of counterfeit medicines that contain wrong APIs (table).

Sample	Source	Expected content	Content
Kamagra 100 tablets, 7–08[1]	*Thailand (traveler)*	*Sildenafil 100 mg*	*Chloroquine*[2] *0,8 mg*
Kamagra 100 tablets, 8–08[1]	*Thailand (traveler)*	*Sildenafil 100 mg*	*Chloroquine*[2] *2,4 mg*
Kamagra tablets, 9–08[1]*, tablett 1*	*Thailand (traveler)*	*Sildenafil 100 mg*	*Sildenafil 15,3 mg Chloroquine*[2] *1,1 mg*
Kamagra tablets 9–08[1]*, tablett 2*	*Thailand (traveler)*	*Sildenafil 100 mg*	*Sildenafil 10,8 mg Chloroquine Sulfamethoxazole*
Cialis "new tadalafil" tablets	*China (internet)*	*Tadalafil 50 mg*	*Sildenafil 129 mg*
Tamoxifen 10 tablets	*Slovakia (internet)*	*Tamoxifen 10 mg*	*Sildenafil 2,3 mg*

[1] *Internal laboratory sample number*
[2] *Diphosphate salt*

Kamagra tablets containing chloroquine

Many of previously studied Kamagra-samples have contained the right API (sildenafil). Hence the Kamagra tablets in Fig. 1, containing the antimalarial agent chloroquine, are exceptional. A

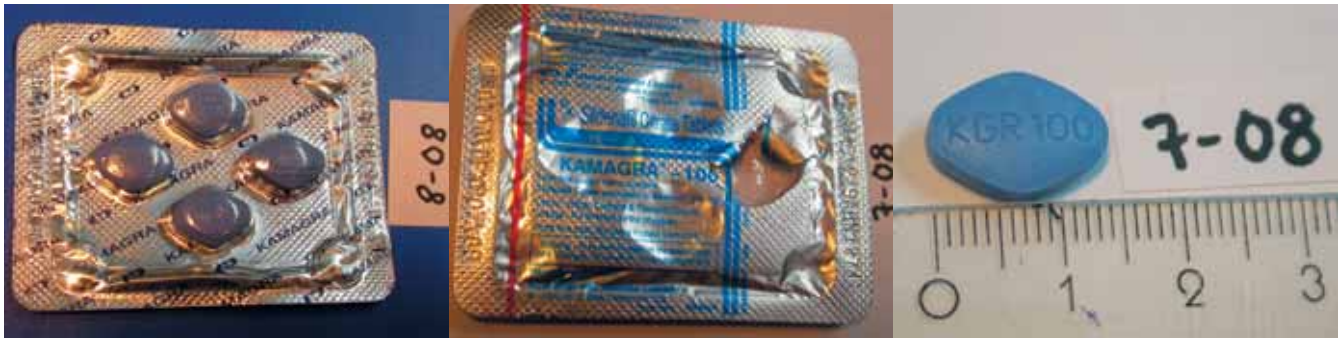

Fig. 1. Kamagra tablets.

warning about Kamagra tablets has been published on the website of NAM (7).

The amount of chloroquine in all investigated Kamagra samples was very low. In samples 7–08 and 8–08 no sildenafil was detected, whereas sample 9–08 contained a small amount of it. In one of the tablets another extra peak, representing an unknown, was detected in the chromatogram (Fig. 2. See figures 2–5 on pages 14–15). The tablet was reanalyzed with a liquid chromatograph coupled to a diode-array detector and a mass spectrometer. On the basis of comparison of retention times, UV- and MS-spectra of the unknown substance in the sample and a reference standard, the extra peak was identified as sulfamethoxazole (Fig. 3).

Cialis from China with Finnish text on the label

Erectile dysfunction medications are one of the most counterfeited medicinal products. The sample analyzed by the Customs Laboratory and the laboratory of NAM was a fraudulent Cialis tablet containing a considerable amount of sildenafil instead of tadalafil (Figs 4 and 5). Although the tablets closely resembled the original ones, the packing was not an imitation (Fig. 6a–b). The label was in English, but surprisingly, the name of the API was also given in Finnish (tadalafiili). The product was probably targeted specially for the Finnish market.

Tamoxifen tablets containing sildenafil only

In this example tablets called "Tamoxifen 10" (Fig. 7) did not contain the antiestrogen tamoxifen, used for treatment of breast cancer, but a low content (2.3 mg) of sildenafil (Fig. 8).

Conclusions

Medicines containing incorrect APIs can be specially detrimental to health, because

- they lack the intended pharmacological effect
- the wrong active pharmaceutical ingredients may cause surprising effects which can be difficult to link to the medicine

There seems not to be any rationale behind producing and marketing counterfeit medicines containing wrong APIs, especially not in producing medicines with very low and sub-therapeutic contents of such substances. For example the Kamagra tablets investigated contained only 1–2 mg of chloroquine (common content is 250 mg/tablet) and the Tamoxifen tablets contained only 2 mg of sildenafil (common content is 25–100 mg/tablet).

The surprising findings described above could perhaps result from

- contaminated production lines
- use of leftovers from production of other medicines/counterfeit medicines
- intentional or unintentional errors in the production of the counterfeit medicines

The examples in this article clearly demonstrate the dangers and problems associated with counterfeit medicines and illegal trade in medicines. To minimize the illegal trade and the resulting safety concerns it is important to continue and further develop the collaboration between authorities in the fight against counterfeit medicines.

See references on page 15.

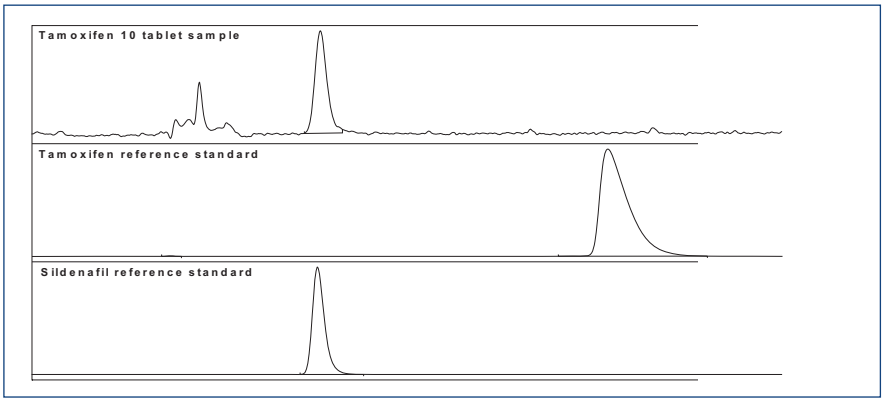

Fig. 8. Chromatograms of a "Tamoxifen 10" tablet sample and tamoxifen and sildenafil reference standards.