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The pharmaceutical sector is constantly developing, but we have seldom seen as many changes under way simultaneoulsy as we will see during this summer season. The Finnish reform of pharmaceutical legislation will lead to the authorities having to revise extensively many decrees, rules and regulations. The much-discussed regulations on the advertising of medicinal products, the restrictions on the importation of medicines by private individuals, and many other issues, which have until now been under the control of the National Agency for Medicines (NAM) only, should then be finalised.

Our state constitution now calls for additional attention with regard to the activities of citizens and entrepreneurs. Mandates for regulations and guidelines must be clear, rules and regulations must be set at the appropriate level, and the powers of authorities shall be clearly enough defined. It is hoped that the reform process will be a success now that the Ministry of Social Affairs and Health will become the principal actor defining and setting up the normative framework in the field of pharmaceutical control. The role of the National Agency for Medicines will be to focus on practical enforcement under the regulatory framework.

Another significant national project concerns the formulation of our pharmaceutical policy, which is currently in progress at the Ministry of Social Affairs and Health. It is reasonable to presume that aspects of our policy will be subject to public debate this coming autumn. The underlying principles of a policy, be it of medicines or any of other field, should point the way to future developments or trends.

There are many goods reasons for formulating a pharmaceutical policy on medicines. In NAM’s view, they include ensuring drug safety and the availability of medicines, Finland’s objectives and profile as a participant in the activities of the EU in the field of medicines control, and in defining the basic principles of retail pharmacies and their operations. Knowing the preferred directions and trends will make it easier for all actors in pharmaceutical services to function. This is particularly important when trends are partly set by actors external to health policy.

The winds of change are also blowing within the European Union. The European Parliament and the Council of the European Union are dealing with the motion on a reform the legislation on pharmaceuticals, which the European Commission put forward last year. In health care services and for the citizens, the reforms might manifest themselves as faster marketing authorisation procedures for new medicines, and an increasing volume of information on prescription medicines becoming available to the consumer. Whether these reforms will be implemented, remains to be seen in the course of the lengthy legislative process.

Some other developments of the pharmaceutical policy of the European Union are also pending. The G10 Medicines report was recently produced (http://pharma-cos.eudra.org/). It comprises an initiative by a working group under Commissioners Erkki Liikanen (Enterprise and Information Society) and David Byrne (Health and Consumer Protection) to find new ways to promote innovations and competitiveness of the pharmaceutical industry in the EU. The interests of public health and social security were also focused on. The proposals included in the final report cover just about everything of significance to the pharmaceutical industry: The industry’s competitiveness, medicines control, the use of information technology, price control and drug reimbursement systems, generic medicinal products, OTC or self-care products, the relative value and cost-effectiveness of medicines, networking of research activity, creation of incentives, improving the information available to patients, and taking into account the expansion of the EU. Some of these items have already been dealt with by the Commission in its proposal.

Some of the proposals of the G10 report fall clearly within the mandate of member states. Such proposals include the application of drug reimbursement systems, and the promotion of prescribing and dispensing of generic medicines. It is interesting to note that these major issues of pharmaceutical policy in the EU do not seem to include the retail sale of medicines. In the Finnish media, the public debate seems to rate the relative importance of the above issues quite differently.
New or old drugs for the prevention of thrombosis?

The mechanisms of developing arterial and venous thrombosis differ from each other. Arterial thrombosis is initiated by platelets becoming attached to the damaged arterial wall, while venous thrombosis is often brought about by inborn or acquired defects in the clotting-factor-regulating systems. Problems arise under situations where the patient is liable to increased blood clotting, such as in pregnancy or during immobilisation. Malignant tumours, and inflammatory cells which are activated during infection secrete proteases with clotting activity and tissue factor which is a powerful activator of the extrinsic pathway of the clotting system. Inflammation is associated with an increased risk of thrombosis. Cancer has been revealed as a factor underlying idopathic thrombosis in about 15% of cases, usually diagnosed within a couple of months after the thrombosis (1).

The specific clotting system disorders causing arterial thrombosis are, with the exception of phospholipid antigen syndrome, far less significant than those causing venous thrombosis. The classic risk factors of arterial thrombosis are disorders of the lipid metabolism, hypertension, smoking, stress and diabetes or insulin resistance, which promote atherosclerosis of the arterial wall and activate platelet function. Topical arterial wall inflammations as well as more generalized inflammations increase the risk of arterial thrombosis. Furthermore, it is often unusually difficult to treat arterial thrombosis in a patient whose arteries are affected with atherosclerosis and whose circulating blood is simultaneously prone to clot due to thrombophilia (2).

In thrombophilia, the blood clotting reaction exceeds its capacity to compensate. As many as 70% of patients with thromboembolism have underlying thrombophilia (3). Its most common hereditary causes are mutations in the genome affecting the clotting Factor V (FV Leiden) and prothrombin. Direct deficiencies in the quantity of clotting regulators are rarer. Acquired phospholipid antigen syndrome, either alone or in association with infection, vasculitis, cancer or drug effects, also explains about a fifth of the occurrences of venous thrombosis. Homocystinaemia, which increases the liability to arterial and venous blood clotting, is especially common in vitamin B₆, B₁₂ or folic acid deficiency. This especially affects elderly patients who smoke and are suffering from extensive atherosclerosis. Administration of vitamin supplements to patients with a thrombotic predisposition is important (4). It would be helpful if the pathogenetic mechanisms were to be determined prior to selecting the medication for inhibition of the thrombotic predisposition.

Antithrombotic treatment alternatives

Platelet inhibitors such as acetylsalicylic acid (ASA, 50–325 mg) and clopidogrel (75 mg) are effective in the prevention of recurrences of arterial thrombosis. Warfarin (INR target 2.0–3.0) and low-molecular-weight heparin are most effective in the prophylaxis of venous thrombosis. In patients with atrial fibrillation and/or impaired left ventricular function (EF below 35%), warfarin (INR target 2.0–3.0) will be effective because clots develop in a situation of stasis. Clots embolised from the aortic arch are also of a similar type due to the circular flow forces targeted at the wall, and warfarin will be effective in these situations, too. The same applies to embolisms despatched by an artificial cardiac valve, but they require stricter anti-coagulation (INR target 2.5–3.5).

The treatment of patients with a special predisposition to the risk of thrombosis should also include ASA (50–100 mg), since platelets are activated in the flow conditions of the artificial cardiac valve. Combination therapy nevertheless requires careful monitoring of the patient (drug interactions, INR, thrombocyte count and anaemia), as the risk of haemorrhage is increased, particularly in elderly patients.

For primary prevention of atherothrombosis, ASA is recommended at a dose level of 50–100 mg in individuals especially at risk (e.g. those with type 2 diabetes). The platelet-inhibiting effect of ASA may be limited in some patients, but part of its effect is to curb the development of inflammation. It is debatable whether a dose of 50–100 mg is sufficient if a potent inflammatory reaction is present in the vascular wall. The co-administration of ibuprofen or indomethacin is not appropriate with aspirin because the platelet inhibiting effect of aspirin would be significantly reduced (5). In a patient prone to haemorrhage, cox-2-selective coxibs may be tried as an analgesic because they do not impair the platelet function.

Clopidogrel, a platelet ADP-acti-
viation inhibitor, should be intro-
duced if the patient does not tolerate
ASA in general or the patient’s other
risk factors are under control and an
atherothrombotic event occurs de-
spite the administration of ASA. A
combination therapy of ASA and
clopidogrel for 3–4 weeks is used as
follow-up treatment after arterial
stenting to prevent (sub)acute
platelet-induced thrombosis. Three
months up to one year following un-
stable angina pectoris the combina-
tion therapy of ASA and clopidogrel
prevented about 20% of the throm-
bolic events of coronary artery dis-
ease compared with a control group
of patients on ASA alone (6).

If thrombosis recurs despite an
appropriate INR level, the question
becomes one of an exceptional pre-
disposition to thrombosis, where the
cause is a combined congenital
and/or acquired defect. There is of-
ten an underlying phospholipid anti-
gen syndrome, in which case the
thrombosis would recur despite war-
farin being in the target region of
2.5–3.5 and ASA having been added
to the therapy. In this case warfarin
should be replaced by permanent
subcutaneous low-molecular-weight
heparin. Treatment-resistant predis-
position to thrombosis occurs in
cancer patients, and on-going stud-
ies will determine the effect of con-
tinuous low-molecular-weight he-
parin therapy on the mechanisms
promoting the progress of cancer as
well as on the liability to thrombo-
sis.

Considerable improvement is re-
quired in the prevention of liability
to thrombosis in association with
surgery. The fact still remains that
about 25–45% of patients with deep
vein thrombosis or pulmonary em-
bolism have actually undergone a
surgical operation during the pre-
ceding month (7). Thrombotic pro-
phylaxis is absolutely necessary in
orthopaedics, extensive cancer
surgery in the hip or abdominal
area, and even with laparoscopy.
The benefit of long-term prophylax-
is (4 weeks) has been especially
proven in arthroplasty of the hip
and the knee, and in cancer surgery
(8,9). The most recent addition to
the treatment of thrombotic prophylax-
is is the selective clotting Factor
Xa inhibitor, fondaparinux, which
improves the AT3 function. The effi-
cacy of fondaparinux is twice that
of enoxaparin when their use for
thrombosis prophylaxis has been
compared (10).

New thrombin-inhibitors which
would replace warfarin in long-term
thrombotic prophylaxis are expected
to be introduced. On-going phase III
trials will evaluate the efficacy of
oral ximelagatran in thrombotic
prophylaxis and treatment, and in
the prevention of thromboembolic
complications associated with atrial
fibrillation.

Studying procoagulant properties
of adhesive platelet receptors and
membranes could be helpful in the
future. It should be possible e.g. to
identify patients responding poorly
to aspirin and to optimise anti-
 thrombotic treatment following arte-
rial thrombosis.

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The main individual health risk among Finns is the use of intoxicants, especially alcohol. The overall consumption of alcohol in 2001 amounted to about 9.2 litres of absolute alcohol per inhabitant and it appears to be steadily on the increase. Nearly 90% of Finns drink alcohol. The mid-European wine-drinking culture does not seem to have become a substitute for our alcohol-drinking habit, the actual aim of which is purely intoxication, but appears instead, simply to supplement the customary habitual drinking. Besides the direct effects that alcohol has on our health, alcohol consumption on this scale will also increase the indirect harmful effects including the problems arising from various concurrent medications and other interactions.

Heavy users of alcohol
A person drinking in excess of four restaurant doses of alcohol per day can be considered a heavy user. The number of heavy users in Finland is probably 300,000, and the majority are in active working life. Absenteeism from work due to ill health among heavy users is double compared with that among normal consumers, and the number of appointments they make with their doctors and days of hospitalisation are seven-fold in comparison. Heavy users also have a seven-fold mortality risk compared with the normal population. About 2,500 people annually die in Finland as a result of alcohol consumption. Alcohol poisoning is the most common cause of death by poisoning in Finland with an approximate annual death toll of 500 people. Alcohol is the cause of a significant number of accidents and violent crimes.

Alcohol-induced diseases
The most common alcohol-induced diseases affect the nervous system (dementia, Wernicke-Korsakoff’s syndrome, cerebellar degeneration, polyneuropathy) and alimentary tract (gastritis, hepatitis, cirrhosis of the liver, pancreatitis). Alcohol also affects the haemopoietic tissue, immune system and hormonal balance. In 2000, about 26,000 people suffered from an alcohol-induced disease which required hospitalisation.

Medical treatment of alcohol dependence
Alcoholism is a chronic recurring state with an underlying development of tolerance and obsessive need to have alcohol. We no longer speak of physical and mental dependence, but of pleasure-seeking behaviour which is controlled by the mesolimbic-hypothalamic dopamine-induced reward-and-pleasure system of the brain, the most important anatomical constituent of which is the nucleus accumbens. The pleasurable sensation will undergo considerable neurochemical change in this centre, and by influencing it, we can also influence alcohol consumption.

The development of treatment methods in alcoholism in recent years has been rapid. The treatment is based on various models of functional and cognitive-behavioural therapy, treatment of co-existent diseases and withdrawal symptoms, and the medical treatment of dependence. Inadequacy of medical proof based on evidence of the efficacy of the various therapies is a problem. Controlled Antabus therapy has proven to be effective in some alcoholics. Drugs available in many European countries specifically aimed at alcohol dependence include naltrexone, nalmefene and acamprosate. The anti-emetic, ondansetron (selective 5-HT3 antagonist), has been used in the treatment of alcoholism.

Naltrexone is an opiate antagonist which has proven effective not only in the withdrawal treatment of narcotics abuse but also in the treatment of alcoholism. The medical costs of naltrexone in the treatment of alcohol dependence in Finland are only reimbursed if the drug is used as part of other treatment, at approved doses and in approved circumstances. Naltrexone used in conjunction with a re-educational therapy will reduce the frequency of relapses in patients who are motivated towards their treatment. After regular treatment over a couple of months, naltrexone taken as required will also abate the urge for alcohol relatively well. Naltrexone therapy has not been associated with especially complicated adverse effects.

Medical treatment of actual alcoholism is at present limited. Considering the rapid development of neurobiology it is likely that highly selective drugs aimed at the treatment of dependence will become available within a few years.
Incapacity for work caused by alcohol consumption

The harmful health effects of alcohol are also reflected in the number of people retiring each year on disability pensions due to alcohol-induced diseases. An individual can be considered incapacitated for work due to alcohol consumption if he or she suffers from alcohol-induced organic or mental diseases due to which the ability to function is permanently reduced, or if the alcohol dependence is otherwise so severe that it is unreasonable to expect the individual to return to work.

An individual who would be able to work if he or she did not drink alcohol cannot be considered entitled to a disability pension. Statistics of 1994–1999 show that the number of entitlements to disability pensions due to alcohol abuse has increased steadily, amounting to about 3.5% of all disability pensions at present. The true share of the number of disability pensions where alcohol is the cause is nevertheless higher than is shown in the statistics, since alcohol-induced diseases are often masked by other diseases and alcohol consumption is often concealed.

Alcohol and the career

The connection between the individual's alcohol consumption and career is interesting. The LEL (Temporary Employees) Employment Pension Fund in Finland offers employment pension security in the building, forestry, agriculture and harbour sectors. 11% of all entitlements to disability pensions due to alcohol abuse have increased steadily, amounting to about 3.5% of all disability pensions at present. The true share of the number of disability pensions where alcohol is the cause is nevertheless higher than is shown in the statistics, since alcohol-induced diseases are often masked by other diseases and alcohol consumption is often concealed.

How to treat the problem of alcohol at the level of the society?

From the national health point of view, heavy consumption of alcohol is a considerable health risk which according to available forecasts will continue to expand. Reduced tax on alcohol as required by the EU, for example, will have an effect in this direction. The opportunities for dissemination of health information have been exceptionally good in Finland. Our occupational health services and health centre system are among the most wide-ranging in the world. Training in the issues of alcohol-related diseases has been organised at the universities for a long time. It has been possible to obtain special competence in addiction medicine since 1994 and the addiction service network in the country is relatively far-reaching. Our knowledge about alcohol-related health hazards has increased exponentially and Finland is a world leader in the research into alcohol-related issues.

Why, then, are the harmful effects caused by alcohol continually growing? The ineffectiveness of the measures available is reflected in, for instance, the increasing consumption of alcohol among doctors themselves which in a way will set an example for the community. Collective control has proven effective previously: the number of deaths from cirrhosis of the liver was considerably reduced during the prohibition act. Would education of the type provided by the example of ‘Turmiolan Tommi’ [a figure used in the past as a national deterrent and a warning] be better than the present liberal attitude? The ball is in the court of the politicians.
There are at least three isoforms of nitric oxide-synthesising enzymes (nitric oxide synthase, NOS): endothelial eNOS, nNOS in the nervous system and inducible iNOS (increased expression in inflammation and other pathological processes). In the circulatory system eNOS maintains vasodilation and inhibits platelet activation and cell adhesion to the vascular wall. In animal models it has been found to inhibit the development of atherosclerosis, and its deficiency may predispose to diabetes. In the peripheral nervous system nitric oxide is involved in nociception and acts as a NANC (non-adrenergic non-cholinergic) transmitter. In the brain NO affects e.g. the vascular autoregulation; but excess amounts of nitric oxide may also cause neurodegeneration.

Nitric oxide in common diseases
Nitric oxide -mediated vasodilation is reduced in, for example, hypertension, diabetes, hypercholesterolaemia, renal insufficiency and in people who smoke. Vasodilation is also reduced by even a mild systemic inflammation; a distinct reduction in vascular relaxation has been detected following vaccination.

High concentration of the endogenous NOS-inhibitor, asymmetrical dimethylarginine (ADMA), is associated with renal insufficiency, hypercholesterolaemia, insulin resistance and, as a study of males in eastern Finland revealed, acute coronary events (1-5). The ADMA concentration in spinal cord fluid is reduced with age, and has been found to be considerably lower in Alzheimer patients than in control subjects of the same age, which is an indication of a link between the increased production of NO and neurodegeneration (6).

Nitric oxide in the skin
The skin produces nitric oxide both via NOS and non-enzymatically (the nitrate in sweat is reduced to nitrite which in the acidic environment of the skin surface leads to NO production). It takes part in cell differentiation and development, healing of wounds and the maintenance of homeostasis and skin barrier function, particularly inhibiting microbes (NO-sensitive in vitro are e.g. Herpes simplex, Propionibacterium acnes and staphylococci, including MRSA). Treatment of tinea pedis and the mollusca with a nitric oxide-releasing ointment has been successful in small controlled studies (7, 8).

NOS is present in excess in inflammatory skin diseases and the anti-inflammatory effect of corticosteroids may be mediated partly through inhibition of nitric oxide. Nitric oxide takes part in melanogenesis, and together with PGE2 it is an active mediator of sunburn erythema; its effects are both cytoprotective and cytotoxic. The over-expression of NOS appears to be related to the development of keloids and to correlate with the degree of malignancy of dermal tumours (9).

Inhaled nitric oxide
Inhaled nitric oxide has been in clinical use for about ten years. It has been used to improve gaseous exchange and to reduce the pulmonary vascular constriction. The biggest benefit is shown in the treatment of neonatal respiratory disorders and pulmonary hypertension, where 15–20 ppm NO inhalation has reduced the need for respiratory equipment, but not the mortality (10). The treatment is not harmless: high NO concentrations may cause methaemoglobinemia, and rapid withdrawal of NO inhalation may cause hypoxaemia and exacerbation of pulmonary hypertension. Studies on the long-term effects of inhaled nitric oxide are under way.

Nitric oxide is also used on other pulmonary indications, though there is no proof of benefit. Pulmonary oedema associated with mountain sickness may be a possible therapeutic indication. People living high in the mountains develop more nitric...
oxide in their lungs than those living on lower ground, which may be one of the factors protective against pulmonary oedema.

**Anti-inflammatory analgesics of the future – more nitric oxide?**

Nitric oxide-releasing anti-inflammatory analgesics (NO-NSAID) have in animal studies been shown to reduce gastrointestinal toxicity of conventional NSAIDs. The protective effect is thought to be caused by preservation of mucosal blood circulation and inhibition of leucocyte adherence to the vascular endothelium. Healing of ulcers and other lesions is also improved with the NO supplement, and this may be due to increased angiogenesis and possibly also the antibacterial effect of nitric oxide (11,12).

In addition to its toxicity reducing effect, the NO-releasing agent may also increase both the analgesic and the anti-inflammatory effect of anti-inflammatory analgesics. An excessive dose of nitric acid may, however, increase the toxicity targeted at the gastrointestinal tract, and not all NO-NSAID compounds have been found to be equally good.

**Or, less nitric oxide?**

The over-expression of iNOS in inflammation is manifested in inflamed joints, irritable colon and asthma. Selective iNOS-inhibitors have been developed which, in addition to these inflammatory diseases, have been thought to offer opportunities also to treat arthritis, stroke, migraine, sepsis, multiple sclerosis, transplant rejection reaction and neuropathic pain and to include prevention of the development of tumours. The results of studies on the benefits of iNOS-inhibitors are contradictory, since the inhibition of nitric oxide synthesis has proved harmful in some inflammation models. Treatment of sepsis has also produced varying responses: in a phase III trial, a low dose of an iNOS-inhibitor improved the prognosis but a high dose made it worse. Problems are caused by the ambivalent nature of the effects of nitric oxide even in other ways – possible adverse effects associated with iNOS-inhibition and reduction in nitric oxide include, for instance, immunosuppression, atherosclerosis and impaired healing of wounds.

**Literature**


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