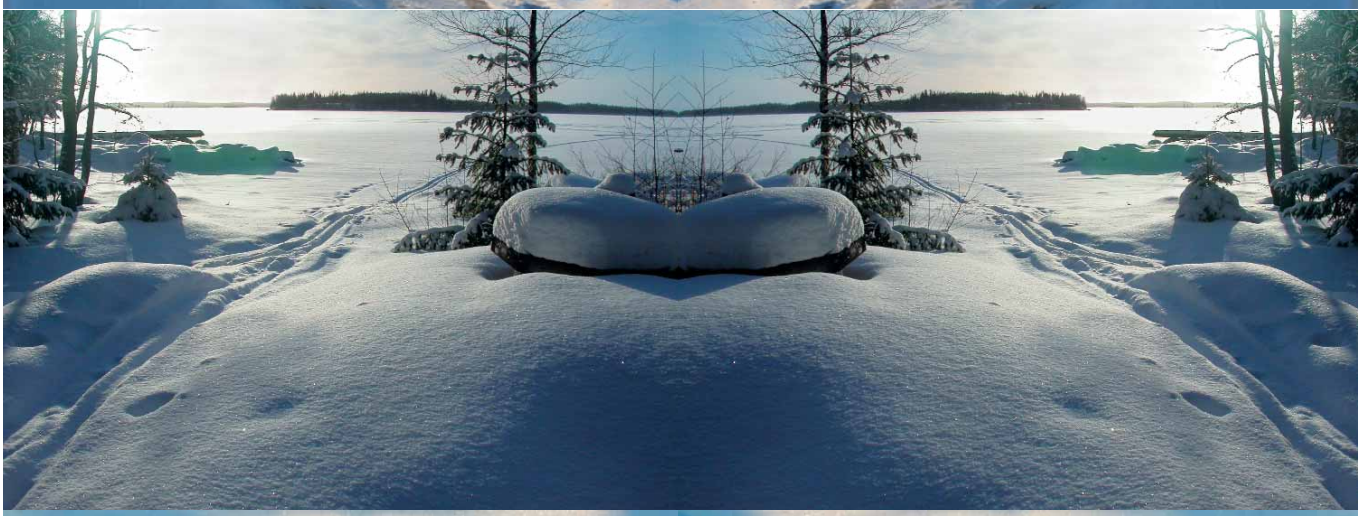
TABU

Lääkeinformaatiota Lääkelaitokselta

Läkemedelsinformation från
Läkemedelsverket, Finland

Drug information from the National
Agency for Medicines, Finland

1 | 2006



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Editorial

The role and credibility of pharmacies, Part II

About seven years ago I wrote in this column about the role and credibility of pharmacy operations.[1] I maintained, for example, that *It seems that the pharmacies harbour plans for increasing their buying power by new co-operation schemes aimed at increasing their profit margins and enabling even more visible campaigns directed at the buying public. The idea that the pharmaceutical industry should compete with discounts for the inclusion of their products in the merchandise of retail pharmacies is outlining the position within the trade.*

At the end of the 1990's there were no intimations of an introduction of generic substitution. Nevertheless, the price discount practices at the time caused concern to the extent that negotiations were held between the National Agency for Medicines, the Ministry of Social Affairs and Health and various pharmaceutical entrepreneurs about the objectives of pharmaceutical advertising and standardised pricing of medicinal products. The negotiations apparently did not lead to a common commitment. In my editorial article at the time I was only able to refer to the legal reforms which would possibly have been necessary unless the issues were to be resolved satisfactorily in some other way.

A mention of the price discounts was nevertheless included in the document Pharmaceutical Policy 2010 of the Ministry of Social Affairs and Health.[2] According to the document, any discounts that are to be implemented will benefit the whole population, and the discounts should be available at a standardised rate to all pharmacies and thereby also to their customers.

The generic substitution in 2003 resulted in the discount practices used by the pharmaceutical industry and pharmacies also being applied to prescription-only-medicines. The situation blew up into an unprecedented media storm in the spring of 2005. In its review to the Ministry of Social Affairs and Health, the National Agency for Medicines maintained that the Medicines' Act had not been violated. The central role played by the pharmacies in the successful introduction of generic substitution has not been denied. The public image of pharmacies had nevertheless suffered a considerable blow.

The legislator has now given his verdict. According to the Medicines' Act reform, the wholesale price of medicines must be universal to all pharmacies and their subsidiaries. The wholesale price must take account of all deductions, rebates and other benefits granted to pharmacies and their subsidiaries.

The government argued for its proposal (HE 107/2005) by stating for example as follows: *The prohibition of discounts to individual pharmacies improves the efficiency of drug distribution based on health aspects, because the sale of medicines by pharmacies will then, to an increasing degree, consider the needs of the customers in protecting their health.* In its report, the Constitutional Committee of the Parliament stated (PeVL 56/2005) as follows: *The regulation fulfils for its part the responsibility prescribed by law, Section 19, Subsection 3 of the Constitution, for the official authority to promote the health of the population.*

It should now be clear to all parties in the pharmaceutical sector that the most important merit of the Finnish pharmacy system in operating as it does, under special regulations, is associated with a pharmaceutical distribution which is based on aspects of health. The responsibilities are stipulated in the Medicines' Act. The State is responsible for the financial framework of the system. The principles are equal for all pharmacies, whether they are large or small, or part of any retail chains or not, and whether their owners are independent pharmacists or universities.

[1] TABU 1/1999, p. 4.

[2] Pharmaceutical Policy 2010. Ministry of Social Affairs and Health 2003:11

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Epidemic nephropathy

Epidemic nephropathy is an acute infection caused by Puumala virus of the hantaviruses group. Hantaviruses are enveloped RNA viruses and are found everywhere in the world. Haemorrhagic fever with renal syndrome is caused by Dobrava, Saaremaa and Puumala viruses in Europe and Hantaan and Seoul viruses in Asia. Hantavirus pulmonary syndrome is found on the American continent and is caused by, for example, Sin Nombre and Andes viruses.

Each hantavirus lives in nature in its own host rodent. Finnish researchers detected in 1980 that epidemic nephropathy is caused by a virus (*Clethrionomys glareolus*) found in bank voles, and the virus was named in accordance with the location where it was found. Humans can contract Puumala virus through bank vole droppings, apparently via the airways. Epidemic nephropathy has not been found to be transmissible from human to human.

About 1,000 serologically confirmed cases of Puumala virus infection are found in Finland every year. The seroprevalence of the virus in the population is about 5% (even 11% in eastern Finland), and the frequency of serologically confirmed cases of epidemic nephropathy is 19 per 100,000. It can consequently be deduced that the number of serologically undiagnosed cases is about six times higher than those diagnosed. A number of the diagnoses of epidemic nephropathy are evidently made on the basis of the typical clinical picture without being serologically confirmed, but a high proportion of the cases probably remain undiagnosed due to the lack or insignificance of symptoms. The highest prevalence of the disease is found in eastern and central Finland with the majority of the cases occurring between August and January. Two thirds of those contracting the disease are men. Animal researchers, forest workers and farmers are some of the risk groups. The disease is rarer and milder in form in children compared to adults.

The pathogenesis of epidemic nephropathy still remains mostly unsolved. The characteristics of all hantavirus diseases include increased capillary permeability, and it is consequently suggested that the target of the virus would be an endothelial cell. Hantaviruses do not, however, cause cell destruction, and it is presumed that cytotoxic T cells with immunological mechanism play a part in the pathogenesis.

Clinical picture

The most common symptoms and findings of epidemic nephropathy can be found in Tables 1 and 2.

The incubation period of epidemic nephropathy is between 2 and 4 weeks. The clinical picture is very varied. The majority of people infected with Puumala virus exhibit symptoms which are quite mild, but in some individuals the disease may be severe to the extent that intensive care is required. It has been found that the host's immune response plays a part in the course of the disease. The alleles HLA-B8 and HLA-DRB1*0301 (DR3) of the human leukocyte antigen system have been found to be associated with severe epidemic nephropathy. Hypotension occurring in the initial stages of the disease and severe renal failure are particularly associated with this tissue type.

The most common symptoms include rapidly rising high fever, headache, nausea, vomiting, and abdominal and back pain. The pain may be so severe that meningitis or appendicitis, for instance, may be suspected at first. Hypotension or even a shock may occur in the initial stages of the disease. About a third of the patients experience visual disturbances, whereas the transient short-sightedness characteristic of epidemic nephropathy only occurs in a small number of patients. The onset of obscured vision is rapid and associated with the fever stage. The vision is restored to normal within a few days.

A few days after the onset of fever the urinary volumes are reduced, and a transient, acute renal insufficiency of varying severity occurs. In fact, the condition may be associated with a severe fluid retention, even pulmonary oedema. A great increase in the urinary volume occurs in the stage of recovery. Polyuria may occasionally be found without the preceding oliguria, which is an indication of a disturbance of renotubular function.

Despite the fact that it is a question of a haemorrhagic fever, with thrombocytopaenia being a common finding, haemorrhages are rare. Transient conjunctival sugillation, epistaxis, macroscopic haematuria, dermal or mucosal petechiae and bleeding at the site of injection may occur. Gastrointestinal haemorrhage is also a possibility.

Epidemic nephropathy is a generalised infection, and the symptoms and findings in a patient may occasionally be atypical. Rare phenomena have

Table 1. Symptoms of epidemic nephropathy

Symptom	Frequency (%)
Fever	98–100
Headache	62–90
Back pain	54–82
Abdominal pain	43–67
Nausea/vomiting	58–84
Myalgia	27–69
Oliguria (<400 ml/day)	54–70
Polyuria (>2000 ml/day)	97
Visual disturbances	12–36
Diarrhoea	12–20
Cough	6–32

Table 2. Laboratory findings in epidemic nephropathy

Finding	Prevalence (%)
Leucocytosis >10.0 x10^9/l	23–57
Thrombocytopaenia	75
Proteinuria	94–100
Haematuria	58–87
Elevated creatinine	86–96
Elevated CRP	52–60
Elevated liver enzymes	41–60
Hypoalbuminaemia/hypoproteinaemia	24–64

been reported in the disease, such as perimyocarditis, meningoencephalitis, hepatitis, acute disseminated encephalomyelitis and Guillain-Barré syndrome.

The prognosis of epidemic nephropathy is considered to be good. The patients usually make a total recovery, but tiredness, for example, may continue for several weeks after the acute stage. Rare long-term adverse effects following epidemic nephropathy have been described, e.g. panhypopituitarism and chronic glomerulonephritis. The mortality rate is highly insignificant (0.1%). Disseminated intravascular coagulation syndrome (DIC), haemorrhage into and necrosis of the hypophysis, and haemorrhage in other organs, have also been described in association with death. The mechanism of death may also be shock or pulmonary oedema.

Laboratory and X-ray findings

The typical laboratory findings in a patient suffering from epidemic nephropathy include protein-uria, microscopic haematuria, thrombocytopaenia, leucocytosis, elevated plasma creatinine, C-reactive protein (CRP) and liver enzyme concentrations, and hypoalbuminaemia (Table 2). In the initial stages of the disease, as a sign of haemoconcentration, high haematocrite levels may occur, but as the disease progresses transient anaemia often develops. Electrolyte disturbances are common, but their clinical importance is usually minor.

A third of the hospitalised adult patients are found to have changes in the lung X-ray: pleural fluid, shadows in the pulmonary parenchyma and, albeit seldom, pulmonary oedema. The changes have been found to be linked with the compli-cations of renal insufficiency and fluid retention. Ultrasound examinations show enlarged kidneys, and pleural, pericardial or perirenal fluid accumulation. An electrocardiogram also shows transient abnormal findings, such as T inversions and ST segment changes.

Diagnosis

The diagnosis of epidemic nephropathy is based on the clinical picture and serology. The diagnosis is made on one serum sample by using immunofluorescence and/or enzyme immunological techniques. Already at the initial stages of epidemic nephropathy, and on the 6th day of illness at the latest, most patients are found to have antibodies of class IgM and usually also of IgG against the Puumala virus. Negative IgG and IgM results exclude epidemic nephropathy. A positive IgG result and a negative IgM result are an indication of a previous epidemic nephropathy.

Lifelong immunity follows a hantavirus infection. A recurrence of epidemic nephropathy has never been seen. A differential diagnosis should take into account any infection (especially sepsis) caused by other viruses and bacteria and other conditions causing acute renal failure as well.

Treatment

The treatment of epidemic nephropathy is symptomatic, consisting essentially of treatment of pain and control of the fluid balance. Fluid therapy requires precise individual adjustment. On arrival at hospital the patient may suffer from hypotension and hypovolaemia, but careless administration of fluid may quickly result in pulmonary oedema, especially if the patient suffers from oliguric renal insufficiency at the same time. About 5% of hospitalised patients need to undergo dialysis. Pain-relieving medication is also required. Paracetamol is an appropriate analgesic, but anti-inflammatory analgesics should be avoided since they impair renal function.

Mild cases can be treated in outpatient care facilities. On suspicion of epidemic nephropathy it is nevertheless recommended that the patient is sent for hospital treatment. Hospitalisation at least is required if the patient's general condition is poor, if the patient evidently suffers from dehydration, fluid retention, oliguria, or renal insufficiency, or if the diagnosis cannot be confirmed.

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My own observation of an adverse drug reaction

Milk protein of an anti-asthmatic is the cause of exacerbation of milk allergy symptoms

Milk allergy is one of the most common food allergies, affecting about three per cent of infants. In the majority of patients the symptoms will have disappeared by school age. Hypersensitivity to milk also occurs in a small proportion of the adult population. It is exhibited in the form of skin symptoms (atopic rash or, less frequently, urticaria), intestinal symptoms (eructation or vomiting, diarrhoea and children's colic), airways symptoms (rhinitis, cough) and, in exceptional cases, even anaphylactic reaction. Milk allergy is often also associated with other allergies. Atopic tendency also increases the likelihood of asthma.

A common excipient in the powder inhalers used in the treatment of asthma is lactose which may even after purification contain small concentrations of milk protein. The following is a description of a young patient of mine with symptoms of milk allergy developing on the introduction of treatment with a powder inhaler containing lactose as one of the excipients.

My 5-year-old patient was diagnosed with a multiple food allergy and an allergy to cow's milk protein with potent symptoms. The patients also suffered from allergic rhinitis and asthma. The asthma had previously been treated with *Flixotide Evohaler* which was replaced by a powder inhaler, a common practice in paediatric asthma patients of this age. The patient developed urticaria and dyspnoea soon after the introduction of *Flixotide diskus* inhalation powder. Dyspnoea was relieved by *Buventol Easyhaler* administered by the parents. The parents' first suspicion was that the urticaria would be a result of a dietary error until after a couple of weeks of reflection they finally spotted a mention in the *Flixotide diskus* SPC about the milk protein that the powder contained. The symptoms were alleviated when the patient's previous medication was reinstated (*Buventol* was also withdrawn and replaced by *Ventoline Evohaler*). The urticaria and dyspnoea were reversible thereafter.

In addition to the reaction above, the Finnish Adverse Drug Reaction database of the National Agency for Medicines has received reports of two other children who developed symptoms of hypersensitivity while using inhalation powders containing lactose.

One of these reports mentioned milk allergy. A 13-year-old girl, who in addition to citrus fruit and fish allergy also suffered from milk allergy, developed a laryngeal oedema in association with the administration of *Seretide diskus*.

The other one concerned an 8-year-old girl who developed a rash in association with the use of *Serevent diskus* when the dose was 50 microg x 4 (no rash developed at the dosage rate of 50 microg x 2 per day).

The SPC and PIL of *Flixotide diskus*, under the section *List of excipients'* includes a mention of the fact that the product contains lactose monohydrate as one of its excipients. Under the same section there is a mention in brackets that the excipient contains milk protein.

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The use of antidiabetic agents in children in 2004

In 2004 there were about 220,000 diabetics (over 4% of the population) in Finland, 31,000 of whom suffered from type 1 diabetes and the rest from type 2 diabetes [1]. A total of 161,305 diabetics in the country were entitled to a special refund of their drug expenses [2].

In 2004, the prevalence of type 1 or juvenile-onset diabetes in Finland was the highest in the world [3]. Infantile diabetes is usually of type 1, but type 2 is constantly on the increase even in young patients. At the end of 2004, a total of 3,478 children under the age of 15 were entitled to a special refund of their antidiabetic drug expenditure [4].

Type 1 diabetes is usually treated with insulin [5]. The most important recent changes in the pharmaceutical care of diabetes include fast-acting insulins (lispro and aspart, A10AB04/05), long-acting insulin glargine (A10AE04), and the insulin pump, which is programmed to administer either a short-acting human insulin (A10AB01) or a fast-acting insulin as a continuous subcutaneous infusion [6-10]. The biggest benefits of these most recent therapies, especially in the treatment of diabetic children, consist of a reduced frequency of hypoglycaemia and an improvement in the quality of life [6, 9]. As a form of therapy, both the basic insulin–mealtime insulin and insulin pump therapy are highly appropriate especially in the treatment of diabetic children [8]. In 2003 there were 764 insulin pump users in Finland, 207 of whom were children [11].

A survey has been carried out with the object of establishing the drugs that were used in 2004 in the treatment of diabetes in children under the age of 15 and determining the distribution of the use and costs of insulin therapies in the country by district, age, gender and mother tongue.

The survey was carried out as a register-based survey. The ATC group of short-acting insulins and analogues was divided into short-acting human insulins (A10AB01) and fast-acting insulins (A10AB04 and A10AB05) in the analysis.

Medicines

The survey material covered 1,460 diabetic children under the age of 15 (42% of those with entitlement to special refunds at the end of 2004). Judging from the survey material, diabetes is slightly more common in boys, in children with Finnish mother tongue, and in children living in small or medium sized municipalities, in comparison with girls, children with a mother tongue other than Finnish or Swedish, and children living in large municipalities.

Insulin was used in all the children in the survey except for two 10–14-year-olds, who were receiving oral blood glucose-reducing drugs (metformin), i.e. they are likely to suffer from type 2 diabetes. Five of the most common diabetic therapies in children under the age of 15 are shown by age groups in Table. They display the drug therapies of 1,140 children (78% of the survey material). The children were usually treated with a short-acting human insulin and/or a fast-acting insulin and a long-acting insulin and/or insulin glargine (1,079 children), i.e. a fairly typical basic insulin–mealtime insulin therapy. The differences in medications between the age groups were minor, but the drug combinations were usually the same in all the age groups (Table). The drug therapies did not differ significantly between the genders. An appraisal by age group showed a small difference in that 0–4-year-old girls were treated with insulin glargine slightly more often than boys of the same age.

The most common single drug therapy used was a combination of a short-acting human insulin and a fast-acting insulin. According to the records, 379 children (26%) of the total number had administered to them either a fast-acting insulin (55 children) or a combination of a short-acting human insulin and a fast-acting insulin (324 children) as the only drug therapy. It is likely that these patients had been receiving concomitant therapy with an NPH insulin or a long-acting analogue in accordance with normal therapeutic practice. Insulin detemir, for example, was introduced on to the market in August and was placed in the basic refund category at the beginning of December 2004, i.e. its use will not show up in the records of the Social Insurance Institution before December. The drug consumption statistics of NAM show, however, that insulin detemir has been sold by pharmacies to the value of about EUR 36,000 in 2004. It was sold with the purpose of compassionate use in the treatment of two children and eight adults only during the same year. The prices of all NPH insulins and insulin glargine exceeded the deductible of EUR 5 per purchase, i.e. they have not been excluded from the data because of their affordability. It remains unclear, therefore, where these patients have obtained their insulin from in 2004.

It is not possible to distinguish insulin pump users in the patient data, because, in addition to the fast-acting insulin used in the pump they should usually also have some sort of system in place to cover for the duration of maintenance or breakage of the pump. Consequently, they should presumably yearly make at least some purchases of a long-acting analogue or an NPH insulin.

Age	Pos.	Drug therapies	Number of users	%	Median cost EUR/person
0–4 y					
	1	Short-acting human insulins (A10AB01) + long-acting insulins (A10AC01)	31	34	231,6
	2	Short-acting human insulins (A10AB01) + fast-acting insulins (A10AB04/05)	19	21	278,5
	3	Fast-acting insulins (A10AB04/05) + long-acting insulins (A10AC01)	11	12	263,1
	4	Fast-acting insulins (A10AB04/05) + insulin glargine (A10AE04)	10	11	385,7
	5	Short-acting human insulins (A10AB01) + fast-acting insulins (A10AB04/05) + + long-acting insulins (A10AC01)	7	8	218,2
5–9 y					
	1	Short-acting human insulins (A10AB01) + fast-acting insulins (A10AB04/05)	165	34	378,9
	2	Short-acting human insulins (A10AB01) + long-acting insulins (A10AC01)	97	20	308,0
	3	Fast-acting insulins (A10AB04/05) + insulin glargine (A10AE04)	48	10	533,2
	4	Fast-acting insulins (A10AB04/05) + long-acting insulins (A10AC01)	46	10	373,0
	5	Short-acting human insulins (A10AB01) + fast-acting insulins (A10AB04/05) + long-acting insulins (A10AC01)	37	8	514,7
10–14 y					
	1	Fast-acting insulins (A10AB04/05) + insulin glargine (A10AE04)	255	29	879,0
	2	Short-acting human insulins (A10AB01) + fast-acting insulins (A10AB04/05)	139	16	576,0
	3	Short-acting human insulins (A10AB01) + fast-acting insulins (A10AB04/05) + long-acting insulins (A10AC01)	107	12	800,5
	4	Fast-acting insulins (A10AB04/05) + long-acting insulins (A10AC01)	87	10	621,5
	5	Fast-acting insulins (A10AB04/05) + long-acting insulins (A10AC01) + + insulin glargine (A10AE04)	81	9	872,8

Five of the most commonly used antidiabetic drugs by age groups

Costs

The average annual costs of antidiabetic agents for children totalled EUR 626 (n=1,460 with a median of EUR 556). The drug costs relative to girls were higher than those relative to boys of the same age.

The main attention in the costs of antidiabetic agents for children was drawn to the use of insulin glargine due to its relatively high price. The total annual drug costs accumulated by children receiving insulin glargine averaged EUR 843, whereas the costs of the other insulin therapies for children significantly lower, averaging in EUR 521 (p=0.00).

Nearly all antidiabetic agents were included in the higher special refund category of 100% in the year 2004; the patients themselves only paid a fixed deductible of EUR 5 per purchase. The true refund percentage in the entire data after deductibles was 96.4.

Conclusions

The survey analysed the diabetic drug treatment and costs of 1,460 children under the age of 15 in the year 2004. The data showed that they were using a) a fast-acting insulin and/or a short-acting insulin and a long-acting NPH insulin and/or insulin glargine (1,079 children) or b) a fast-acting insulin alone or a combination of a fast-acting and a short-acting human insulin (379 children). Two children were using oral blood glucose reducing drugs.

The average annual drug costs relative to children amounted to EUR 626. The costs accumulated by girls were slightly higher than those by boys, and they increased with age for both groups. The annual drug costs of insulin glargine users were the highest of all.

The differences in medication between the genders were insignificant, but there were significant regional differences in the use of insulin glargine.

See additional figures on pages 35–38.

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Translation Mervi Moisander