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TABU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA

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Summary

Summary

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Influence, transparency and better service

International regulatory control of medicinal products and medical devices is in a state of change. Regulatory agencies are expected to exert more and more influence in the interests of patients and consumers. Decisions, their motivations, and procedures should be transparent. The 'control services' offered to citizens, health care professionals and the industry should be of the best possible quality. These factors have resulted in a reorganisation of the National Agency for Medicines (NAM) and to its functional development.

The major aspects of NAM's process of change – the strategy extending to the year 2006, the reorganisation, and the Results Agreement for 2003 concluded with the Ministry of Social Affairs and Health – have been finalised. It is time to review the concrete objectives of these changes.

In the international control of pharmaceuticals and medical devices, the significance of the contribution of any single state, organisation, or individual may remain indistinct. That is understandable, if the decisions made at European Union level are commonly thought to be made by a distant and obscure organisation, for which nobody has any personal responsibility. In fact, however, each decision has been prepared, presented and executed by appropriate officials, either collectively in joint bodies, or at individual level.

For the control of medicines and medical devices, influence means having real and actual power to exert influence on any decisions of relevance, be it on the national or the common EU level. In terms of medicines control, most significant decisions are ultimately made in international co-operation, although national ad hoc solutions might have been resorted to in the first instance.

For the National Agency for Medicines, exerting influence implies assuming additional responsibility and accepting further functions in the regulatory cooperation. The issues should be important for Finnish health care, and we should have enough top expertise and resources at our disposal. We should ensure that we exert influence at home in accordance with social affairs and health care strategies.

What, then, is transparency in terms of the authorities' operations? I should think it consists mainly of the grounds for the decisions adopted being public knowledge, and the operating principles transparent. That will increase our credibility and public confidence in us. Much remains to be done in this regard, both by the national authorities and EU organisations. Transparency is a growing trend at present, and that is good. The times, when a regulatory body was satisfied with decisions being made formally in the correct order, are something of the past.

National Agency for Medicines is advancing in rapid strides along the road to transparency. The publication on our web pages of SPCs and PILs, of documents circulated for comments, and even of our rules of procedure, are signs of this trend. Rapid progress is being made in Europe towards the publication of all statements of scientific evaluation of medicines, as already practised by EMEA.

The concept of Clients of the NAM has been defined in the Results Agreement between the National Agency for Medicines and the Ministry of Social Affairs and Health for the first time. It is well worth repeating here:

> Citizens needing medicines, medical devices, or blood products are the ultimate clients of the National Agency for Medicines. The National Agency for Medicines maintains and promotes the safe use of the above-mentioned products. In practice, this control focuses on the research, manufacture, sales, distribution, and marketing of medicines and medical devices. In terms of our control function, our primary clients are entrepreneurs within the industry. Health care professionals play a crucial role in the clientele chain.
>
> The control of medicines and medical devices consists to a great extent of co-operation. Our partners include various statutory authorities and bodies, research and testing institutes, international organisations and universities.

The majority of NAM's clients are paying customers. They, as well as all the other clients, are entitled to demand from NAM quality services rendered on time and according to good management principles. The study of interest groups carried out in 2001 gave valuable clues on how to improve our services further. We are now on that road.

Translation Liisa Fellman-Paul

Summary

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The use of stimulants in attention deficit hyperactivity disorder (ADHD) in children and adolescents

In addition to problems of human relationship and difficulties at school, children with attention deficit hyperactivity disorder (ADHD) will also run the risk of developing complications such as anxiety, addiction and an affective syndrome in their later years of life. Besides psychosocial methods of treatment, the treatment of ADHD has consisted of psychotropic drug therapy with stimulants and partly with dual-action antidepressants. This review will focus on the treatment of ADHD and particularly the use of stimulants.

ADHD was reported for the first time in 1901 (see Solanto et al., 2001), and its recognition and treatment have been widely studied ever since. The diagnosis is based on the recognition of the clinical symptoms. The ICD-10 classification of hyperkinetic disorders (Stakes, Finnish Research and Development Centre for Welfare and Health, 1997) is outlined in Table 1. The diagnostic classification DSM-IV is accepted as the appropriate classification to use in USA and is therefore also included in Table 1. Background information on the patient given by the parents and the school is of key importance in the diagnosis. A structured interview can be helpful in the collection of such information (Aronen, 2000). Attention disorder and hyperactivity are considered the core symptoms of ADHD, and the disadvantages become apparent even as early as before the age of seven. A later start for the affliction, at the age of 7–9, has been described in some substates of the disorder (Erkolahti and Piha, 1998, Solanto et al., 2001).

It is suggested that the prevalence of ADHD in 6–15-year-olds is 3–5%. Epidemiological studies show it to be more prevalent and more complicated in boys; boys are reported to be afflicted with the disorder 2–9 times more commonly than girls (Puura et al., 1998). ADHD occurs in two or more life situations, usually at home and at school. It is a long-term disorder associated with significant deterioration in cognitive and social skills and achievement at school. Patients with ADHD are often found to suffer from other concomitant disorders such as learning difficulties, oppositional defiant disorder, anxiety and affective syndrome. Long-term follow-ups have also revealed associated socio-economic complications later in life, and a considerable number of concurrently occurring illnesses, especially in relation to anxiety, addiction, personality disorders and affective syndrome. Antisocial personality disorder and addiction problems may later in life be more usual in children with a behavioural disorder in addition to their ADHD (Biederman et al., 1996, Räsänen 1999). ADHD has been reported to continue into adulthood in 10–60% of patients (Biederman et al., 1993).

ADHD is more common in the close relatives of children receiving treatment than in the relatives of other children, which is an indication of the significance of genetic factors in the development of the disorder (Solanto et al., 2001). Gene studies are focused on the genes, which regulate the dopamine and noradrenaline-mediated nerve function (e.g. dopamine transporter and dopamine-4 receptor genes, and noradrenaline-mediated alfa-2a and -2c receptor genes). This is because the regulation disturbance located in the prefrontal and striatal area of the dopamine system is considered to be of key importance to the development of ADHD. In addition, the regulation disorder of the noradrenaline-mediated nerve function is also of importance as it affects the state of alertness, for example. In fact, the effect of methylphenidate and dextroamphetamine therapy is considered to consist of decreasing both the dopamine and noradrenaline re-uptake in the nerve ends, in

Table 1. Classification of hyperkinetic disorders

ICD-10

F 90.0	*ADHD*
F 90.1	*Hyperkinetic conduct disorder*
F 90.8	*Other hyperkinetic disorders*
F 90.9	*Unspecified hyperkinetic disorder*

DSM-IV

ADHD, combined type
ADHD, mainly attention deficit type
ADHD, hyperactive/impulsive type
Unspecified ADHD

addition to which dextroamphetamine also increases the release of dopamine and noradrenaline (Solanto et al., 2001).

Various psychosocial treatment models have been developed for treating ADHD, with the aim of reducing the disadvantages occasioned by the disorder at school and in the family circle (Multimodal Treatment Study of Children with ADHD, or MTA Co-operative Group 1999a). In addition, the use of psychotropic drug therapy with stimulants and to a certain extent also with antidepressants (e.g. desipramine and venlafaxine) has increased in moderate and severe cases. Superior results have been achieved with concurrent use of both therapies above (MTA Co-operative Group 1999b). The stimulants, short-acting methylphenidate and dextroamphetamine, are in use in Finland at present by special authorisation. This review focuses on the results of studies published on the various possible uses of stimulants, particularly in the treatment of ADHD. Other indications for stimulants, such as narcolepsy, treatment-resistant depression or apathy caused by a common illness (AACAP 2002), are not discussed.

Treatment of ADHD

The most important aims in the treatment of ADHD consist of alleviating the behavioural disturbance, and improving the quality of interaction between parent and child and the social skills of the patient. By palliating the core symptoms of ADHD, anxiety associated with the disorder will also be alleviated (MTA Co-operative Group 1999b). The primary alternatives of treatment in mild and moderate cases in the prevailing European clinical practice are psychosocial treatment methods, coupled with medical treatment in severe cases (Aronen 2000). Based on the assessment of the results of the MTA study it could be accepted that medical treatment could nevertheless also be given to patients with an inadequate response to behavioural therapy or otherwise in need of more effective treatment. Concurrent administration of medical treatment and behavioural therapy have proven more effective than behavioural therapy or community therapy alone (Taylor 1999, MTA Co-operative Group 1999a). The drug doses used in combination therapy have been smaller than when using drug therapy alone (MTA Co-operative Group 1999a).

Psychosocial therapy of ADHD

Since the occurrence of ADHD symptoms is influenced both by stress and psychosocial stress factors, various psychosocial treatment methods have been developed, such as support and guidance given to the parents, the child and the school. Based on behavioural therapy, a system of rewarding the desired calm behaviour could also be used, as well as some of the more specific therapies such as cognitive or pscychodynamic individual therapy or family therapy (MTA Co-operative Group 1999a, Aronen 2000). Psychosocial treatment methods are generally approved by families, and the percentage of patients disrupting their treatment in the MTA study (USA), for example, was only 3.5 percent (MTA Co-operative Group 1999a).

Medical treatment

The effectiveness of medical treatment of ADHD with stimulants has proven in several studies to be superior to that of a placebo. The number of patients participating in clinical drug trials has been considerably higher than in other fields of psychiatric therapy, and the efficacy of stimulant therapy can be considered unequivocally as proven. Stimulant therapy is generally not recommended before the age of six. The first symptoms of the disorder may nevertheless appear as early as prior to the age of three. Further studies would be required especially in the treatment with psychostimulants of children of pre-school age.

The USA drug authority FDA approved the use of stimulants for the treatment of ADHD more than 20 years ago. The time- and countryspecific differences in stimulant use vary greatly. For example, in the USA the use of stimulants has increased five-fold during the 1990s, and the differences in the use of stimulant therapy between different countries are significant, being as high as 10 to 30-fold in comparison (Taylor, 1999). In the general discussion on stimulant therapy, concern is expressed about the development of drug dependence later in life; it has been suggested that long-term stimulant therapy is a cause of an increased risk especially of cocaine and nicotine dependence. The results of studies in the field are nevertheless contradictory, and a decreased risk of drug dependence has also been reported. An increased risk of dependence has also been reported in untreated patients or patients with a poor response to treatment (Solanto et al., 2001). About one percent of patients on stimulant therapy in the USA have gone over to the use of drugs, and drug addiction has been most common among adult users of mixed therapies.

The proportion of patients benefitting from stimulant therapy in various trials has been between 65% and 95% when the accepted response criteria included reduced motor restlessness, less disturbed behaviour and improved social relationships. The same studies reported a 4–30% response to a placebo. The state of alertness and reaction time are improved by medical treatment, and the response is dose dependent. Good response to medical treatment can be anticipated when the following criteria are fulfilled: young age, state of low anxiety, higher degree of severity of symptoms and high intelligence quotient. As regards the underlying criteria expected, however, study results vary and the expectations at the level of the individual are unreliable. Response to treatment does not appear to differ between the two sexes (MTA Co-operative Group 1999). Approval of the medical treatment by the patient's family is an important condition of success, and inadequate treatment compliance is considered a contraindication for stimulant therapy (Läkemedelsverket 2002). Previous predictions alleged that the response to stimulant therapy might disappear due to the tolerance developed on long-term use, but this is not confirmed by more recent stud-

ies. Opinions on the necessary duration of stimulant therapy vary, but ADHD is a long-term disorder, which may need years of treatment despite varying severity of the symptoms. Further studies would be necessary on long-term treatment of ADHD, since withdrawal of the medication appears to wipe out the positive effects of the stimulant therapy (Solanto et al., 2001).

Methylphenidate

The drug most commonly used in stimulant therapy is short-acting methylphenidate. The daily dose in different studies has varied between 0.3 and 1.2 mg/kg, and the usual dosage of the short-acting formula has been 3 times daily (at about 8 a.m., 12 noon and 4 p.m.). The interval between administrations should be about four hours to avoid reduced efficacy, and an afternoon dose is recommended to avoid rebound effects due to cessation of the effect of the drug.

One of the biggest impediments to the use of the short-acting formula is considered to be the fact that it ought to be taken during the school day as well, which may make its regular use more difficult. Longer-acting drug forms have therefore been developed to facilitate administration (Pelham et al., 2002). The response to the dose varies significantly between individuals; consequently, individual adjustment of the dose once a month according to the patient's tolerance to treatment and the degree of alleviation of the most complicated symptoms is considered the most appropriate approach in clinical use.

The most common adverse reactions reported for methylphenidate are sleep disturbances, stomach pains, headache, increased irritability and occurrence of involuntary movements or tics. Tics are caused by the dopamine-agonistic effect of methylphenidate and their presence in the patient or the patient's near relatives is considered a contraindication for methylphenidate therapy, even if rare and mild symptoms of tic are not regarded as preventing continued treatment. Stimulants reduce the growth rate, and an interruption of the medication during weekends is therefore recommended. Development of psychosis is very rare, but previous or present symptoms of psychosis are considered a contraindication for stimulant therapy. Other contraindications include glaucoma, hyperthyroidism, hypertension or other symptomatic heart disease or pregnancy (Läkemedelsverket 2002, AACAP 2002). Stimulants have been found to reduce the threshold of spasms, even though this effect is minor with the doses used to treat ADHD. However, the use of stimulants in children with previous epileptic seizures requires concurrent anti-epileptic therapy. Nevertheless, adverse reactions associated with stimulant therapy (Table 2) are generally mild and can be reduced in intensity by a reduction in the stimulant dose. Adverse reactions have caused the withdrawal of stimulant therapy in about 4% of patients.

Other stimulants

Dextroamphetamine has been used somewhat at the dosage rate of 0.15–1.0 mg/kg/day in two divided doses. Tolerance to the cardiovascular, appetite-reducing and mood-lifting effects of dextroamphetamine will be induced in the patient during the weeks following introduction of the drug. Two stimulants (methylphenidate and dextroamphetamine) were used concurrently in individual trials, and the percentage of the patients not benefitting from the stimulant therapy remained at 4%; nevertheless, the concurrent use of two stimulants cannot be considered as common clinical practice.

Table 2. Adverse reactions associated with stimulant therapy

Common reactions

- headache
- stomach pains
- sleep disturbances
- increased irritability
- involuntary movements or tics

Rare reactions

- psychosis
- loss of hair
- rash
- liver damage (pemoline)
- epileptic seizures
- palpitations
- hypertension

Other medical treatments

In addition to methylphenidate, ADHD has also been treated with other drug therapies. In a small trial, the effects of MAO inhibitors, clorgyline and tranylcypromine were shown to be equal to that of dextroamphetamine. However, MAO inhibitors and stimulants should not be used concurrently due to the risk of a hypertensive crisis. Tricyclic antidepressants, chlorpramine, imipramine and desipramine, were shown to be effective in the treatment of ADHD, even though their efficacy was inferior to that of methylphenidate (Wilens et al., 1996). They have the adverse effects of tricyclic antidepressants, and more recently dual-action antidepressants such as venlafaxine have therefore been used as antidepressant medication in ADHD. If intolerance to stimulants occurs, the suggested alternative medication in addition to antidepressants is clonidine; it achieves a slower response, however, compared with the groups of drugs mentioned above. Preliminary trials of other noradrenergic preparations such as tomoxetin have shown themselves to be effective in the treatment of ADHD (Spencer et al., 1998).

Conclusion

Full use of the possibilities offered by the medical treatment of ADHD requires a reliable system of assessment and a setup of guidelines for treatment appropriate for the conditions in Finland. This is especially necessary as the principle of the action of stimulants is different from that of the psychotropic drugs in use at present, and knowledge of the special characteristics of the preparations in the group is required (Erkolahti and Piha 1998, Taylor 1999, Aronen 2000). Medical treatment of this patient group can be facilitated by the new long-acting methylphenidate. Drugs under development with an effect on the noradrenaline-mediated nerve function can in the near future diversify the selection of drugs available at present.

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Summary

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Pain in the oral mucous membranes

Several underlying factors may cause non-specific pain in the mouth and tongue. This article focuses on the most common conditions which cause pain and on the burning mouth syndrome.

Variations in normal anatomy

Fissured tongue, lingua plicata
Fissures can be seen on the surface of the tongue in about five percent of the population. The number of fissures and their depth may vary . Microbial matter readily accumulates in the fissures, and the tongue consequently easily becomes inflamed. Smarting pain occurs in the inflamed tongue, which may even be slightly swollen. The treatment of an inflamed fissured tongue consists of cleansing of the fissures with a toothbrush or by using a special plastic spatula designed for the cleansing of the tongue (1).

Benign migratory glossitis, lingua geographica
Benign migratory glossitis is found in about two percent of the population. It consists of change of unknown origin in the mucous membrane of the tongue and it is occasionally known to be associated for example with stress, oral fungal infection, psoriasis and asthma. Benign migratory glossitis is often also associated with fissured tongue. The clinical signs consist of red, irregular blotches surrounded by a light yellowish edge. The blotches on the tongue typically change place, hence the name migratory glossitis (1, 2).

Benign migratory glossitis is often symptom-free, but certain foodstuffs can occasionally cause smarting (1). No treatment is usually required. A topical mild corticosteroid may be prescribed for smarting lesions if necessary.

Aphthae

After traumata, aphthae are probably the most common cause of oral pain. Depending on the study, the prevalence of aphthae is 20–60% in the population overall. The etiology of aphthae is unknown at present. Several possible factors have nevertheless been studied (Table 1).

Aphtha minor is the most common form of aphtha. The changes of recurrent aphthous stomatitis (RAS) also follow this pattern. Typically, a sore, oval shaped 1-cm lesion is seen, which is covered by yellowish fibrinous coat. Occasionally there may be several lesions at the same time. Changes may occur almost anywhere in the oral mucous membrane, but never on the adjoining gums or the palate. Aphtha minor heals on its own within about a week and does not leave scars.

The lesions caused by **aphtha major** (or Sutton's disease) are bigger than those caused by aphtha minor; their diameter varies between one and two centimetres. Single lesions may occur, or as many as ten of them may occur at the same time in the mouth. The lesions are very sore and slow to heal. Lesions caused by aphtha major will leave scars after healing.

Herpetiform aphtha is the term used for small aphthous lesions (with a diameter of 1–2 mm) occurring in groups. Herpetiform aphtha may occur anywhere in the oral mucous membrane, i.e. including the gums and palate. These lesions heal by themselves within about a week, and do not leave scars.

If the patient suffers from recurrent aphthous stomatitis, the possibility of an underlying systemic disease should be investigated. The patient should be interrogated about other possible symptoms such as those involving the digestive tract, foodstuff allergies, diet, and other more generalized conditions, e.g. bouts of fever. Elderly patients in particular should be examined to establish serum vitamin B_{12}, iron and folate values to exclude anaemia. Unless anything unusual is detected on medical or dental examination, medication may be tried in the treatment of aphthae (3).

Treatment of aphthae is aimed at alleviating the pain and shortening the duration of the lesions. The topical treatments most frequently tried include the application of triamcinolone acetonide, anaesthetising ointments and chlorhexidine mouthwashes. Since the sodium lauryl sulphate contained in most toothpastes may denature the oral mucous membrane and thereby promote the development of lesions, patients with aphthae should avoid the use of toothpastes which contain this compound. Systemic glucocorticoids, pentoxyphylline, thalidomide and

Table 1. Factors possibly underlying the occurrence of aphthae (3)

Deficiencies
vitamins B1, 2, 6, 12, iron, folate
Hypersensivity reactions
e.g. to benzoic acid
Genetic predisposition
Viruses (herpes, measles)
Behçet's disease
Haematological disorders
erythrocyte changes
Gastrointestinal diseases
Crohn's disease, celiac disease, ulcerative colitis
Hormonal factors
menstrual cycle
Trauma
Certain medicinal substances
anti-inflammatory analgesics, chemotherapy
Immune deficiency
HIV, leukaemia
Stress

tetracycline or cephalexin mouthwashes have also been tried on extremely complicated aphthous oral inflammations. It should be borne in mind, nevertheless, that systemic treatment of aphthae is in no way routine treatment (3, 4)!

Deficiencies

Among deficiencies, iron and vitamin B_{12} deficiencies are the most common conditions causing changes and symptoms in the oral mucous membrane. Iron deficiency has an effect on the development and growth of all cells. In the mouth, iron deficiency anaemia is manifested as mucous membrane epithelial atrophy. Typically, this shows up as atrophy of the lingual papillae and stomatitis at the corners of the mouth. Iron deficiency anaemia is treated with oral iron supplements for a period of four to six weeks. The body's iron stores are replenished within just over two months, but the mucous membranes take a longer time to heal (1, 2).

Vitamin B_{12} and/or folate deficiencies cause a disturbance in DNA synthesis. This is manifested as macrocytosis of the oral mucous membrane epithelial cells. The clinical manifestations are usually a red and smooth tongue, which is also painful. Deficiency of vitamin B_{12} is treated with vitamin supplements The cause of deficiencies should also be established, and the possibility of e.g. coeliac disease or pernicious anaemia should be excluded (1, 2).

Common diseases

Several common diseases can cause pain in the oral mucous membranes. A list of these diseases is shown in Table 2.

Lichen planus is a relatively common disease of the skin and mucous membrane, the cause of which is so far unknown. It is nevertheless assumed to be caused by a cell- mediated immune response to either an external or an allogenic antigen. About two thirds of the sufferers are women, and the disease occurs primarily in 40–60-year-olds. In addition to mucous membrane symptoms, 20–60 % of lichen sufferers also exhibit skin changes, and about half the patients with lichen planus also have a secondary fungal inflammation of the mouth. Typically, the skin changes are periodical, but the changes in the oral mucous membranes are long-term. The clinical picture of lichen in the oral mucous membranes is very varied, and it is divided into six main types: papular, reticular or net type, plaque type, atrophic, erosive and bullous type (5). The most common of these is the reticular type, and features of several lichen types are often found in the changes in the mouth. It should be borne in mind that a definitive diagnosis of lichen can never be made on the basis of a clinical manifestation alone, and the diagnosis needs to be confirmed by biopsy.

A frequent symptom of lichen planus is a periodic stinging sensation in the oral mucous membranes. Certain foodstuffs, such as tomatoes and citrus fruit, typically provoke the sensation. The clinical picture of lichen does not always coincide with the patient's symptoms. It needs also to be taken into account that the symptoms of a lichen patient are exacerbated if the patient has an oral fungal infection.

Treatment of lichen planus consists mainly of treating the symptoms and the inflammation. Topical corticosteroids are the therapy most commonly used at present. These are administered as a course of treatment (5). Untreated fungal infection of the mouth is a contraindication to starting corticosteroid treatment of lichen. As there are very few placebo-controlled studies of medical treatment of lichen, the superiority of any one treatment compared with any other is difficult to establish (6).

Table 2. Common diseases, which can cause pain in the oral mucous membranes

Diabetes
Lichen planus
Erythema multiforme
GI-diseases (Crohn's disease, coeliac disease)
Vesicular diseases (e.g. HSV)
Neurological disorders
Connective tissue diseases (e.g. SLE)
Malignant tumours

Burning mouth syndrome

If no explanation for the patient's pain in the mouth is found despite careful studies, it may be a case of a burning mouth syndrome. Patients with a burning mouth syndrome. are typically postmenopausal women, and the majority suffer from anxiety, depression or even personality disorders. The symptom complained of is a burning, symmetrical pain, which is usually located in the tongue. The pain becomes worse towards the evening, but drinking or eating usually alleviates it (7).

Burning mouth syndrome has been treated as if it were a psychosomatic disorder. More recent studies have nevertheless revealed somatic states possibly causing this syndrome. It has been suggested that a large number of papillae fungiformae on the tip of the tongue constitute a predisposing factor for the syndrome. The larger the number of papillae, the more strongly the irritation of the taste nerve experienced. The sense of taste may change during menopause, and these changes can alter the function of the chorda tympani so that its inhibiting effect on the trigeminal nerve is reduced. The trigeminal nerve mediates the sensation of touch and pain from the area of the mouth, and consequently, these sensations are emphasised. Any trauma suffered by the chorda tympani may of course also cause a reduction in the inhibition (7). The fact that the pain is relieved when the area is anaesthetised is also an indication of the neuropathic cause of the pain. Patients with burning mouth syndrome have also frequently been found to have a low vitamin B_{12} level in the blood. It may well be the case, therefore, that anxiety and depression often associated with the disease are after-effects of the pain, and not its cause.

Burning mouth is very difficult to treat. Good results in the treatment of burning mouth have been obtained with vitamin supplements, especially vitamin B supplements (9. Psychotherapy has also been tried as a treatment due to the possible mental component associated with the disease (7).

Conclusion

Pain in the oral mucous membranes is a relatively common ailment. The cause of the pain may well be easily found by taking a look in the patient's mouth. However, more extensive examinations are often more usually required in order to establish the cause. It also needs to be borne in mind that the pain could be a primary symptom of oral cancer.

The treatment of the most common changes in the oral mucous membranes is most practically given by a dentist, but the most complicated cases of mouth pain are attended to in central hospitals, usually in departments for oral diseases. The collaboration of several medical specialists and/or dentists is often required in the treatment of complicated cases of pain.

I would like to express my gratitude to Professor Tuula Salo for her valuable comments.

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Report of an adverse reactions

An insulin-treated diabetic patient, vascular surgery and protamine – a predictable outcome?

What is protamine?

Protamine is the general term for very basic proteins with a molecular weight of 4–7 kDa containing 60% of arginine; they are also bound to the DNA in the germ cells as a so-called nucleoprotamine in almost all vertebrates. In mammalian cells protamine is found only temporarily in the decondensation of the sperm nucleus (Shimada et al. 2000). It occurs especially in spawners such as salmon, trout, herring, cod, sturgeon and mackerel. In men, protamine is found in the nucleus of the sperm (Samuel et al. 1978).

What about protamine sulphate?

Sulphonated protamine is used in insulin to prolong its effect: insulin is tightly bound to it and is then released slowly, which produces "long-acting insulins", especially the so-called NPH insulins. One NPH insulin, for example, contains 0.348 mg of protamine sulphate corresponding to 0.270 mg of protamine base/100 IU of insulin. Protamine is also used as bolus injection in surgery as a heparin antagonist; the most common dosage then used is 1 mg of protamine/100 IU.

What adverse reactions are caused by protamine sulphate?

Anaphylactic shock was one of the first reported adverse reactions of protamine in humans (Nordström L et al. 1978). Later over 100 protamine-induced deaths have been reported in the literature (Tsui et al. 2001). Protamines have been found to be highly immunogenic; subcutaneous insulin injections containing protamine and intravenous injections of even small doses will start the production of protamine-specific IgE and IgG antibodies (Weiss et al. 1989, Nyhan et al. 1996). Adverse reactions of intravascular administration of protamine have included redness of the skin, urticaria, bronchospasm, pulmonary hypertension, systemic hypotension, pulmonary oedema and sometimes, but rarely, even death (Horrow 1985, Weiler et al. 1985). Adverse reactions are transmitted via several various mechanisms, such as type I allergy, complement activation and direct release of histamine (Horrow 1985, Weiler et al. 1985).

Diabetics treated with NPH insulins have been found to be at a 10–30-fold risk of anaphylaxis when heparinisation is reversed (Lewy 1992). The incidence of anaphylaxis in diabetics is in the range of 0.6–2% and mortality as high as 40% (Lewy et al. 1986). Desensitisation of patients with insulin allergy may accidentally also produce IgE-mediated protamine allergy (Bollinger et al. 1999). In infertile and vasectomised men, anti-protamine activity may increase the risk of anaphylaxis (Samuel et al. 1978); the same applies to patients with iodine, shellfish and fish allergies (Kimmel et al. 1998). Patients who have previously undergone vascular operations also have a greater risk of anaphylaxis, but an anaphylactoid reaction without earlier predisposing factors is also a possibility (Peng et al. 2000). Platelet and blood transfusions are nevertheless more frequent causes of adverse reactions in surgery than simultaneously administered protamine (Lewy 1992).

A case study

A 65-year-old female with LADA type diabetes for the past 20 years, and also with mild nephropathy, hypertension, coronary artery disease and cardiac insufficiency.

Three months prior to her hospital visit, small, bluish, blotchy lesions had developed in both her calves surrounded by a highly reddened area of skin and with a tight tectorial membrane over the lesion. The lesions had become larger despite appropriate topical treatment. The patient was hospitalised to improve the topical treatment and to find the cause of the lesions. Prior to results of laboratory tests and biopsies the patient was treated for suspected vasculitis and, after tests respecting her diabetes, she was given prednisolone 20 mg x 1. Vasculitis was not indicated by biopsy results, however, and the dosage of prednisolone was gradually reduced. Despite effective treatment, the lesions became worse during hospital treatment, and an angiography of the lower limbs revealed a diffuse, serious arterial stenosis of the lower limbs distal to the level of the thighs. ASO was established as the cause of the lesions, the predisposing factor being long-term diabetes. Adequate results were not produced by PTA measures, and consequently extensive vascular surgery was performed in the form of arterial bypasses in both lower limbs.

The operation was technically successful, but to reverse heparinisation the patient was given 1 mg of protamine sulphate at the end of the operation, and she thereupon rapidly became extremely hypotensive. The patient's emergency treatment consisted of an intravascular dose of 250 mg of hydrocortisone administered in response to the assumed allergic reaction. The administration of phenylephrine was initiated in order to correct the hypotension, but despite this, the patient's pulse rate was reduced and she quickly lost consciousness. The patient was intubated, assisted respiration was commenced, and the patient was given 2 mg of adrenaline in addition. As a result of the adrenaline the patient developed ventricular fibrillation, which was corrected by defibrillation. The patient was also initially given an infusion of dopamine, which was changed to dobutamine when she was transferred to intensive care. By the following morning the patient had once more had a series of ventricular fibrillations which settled on defibrillation. By this time, the patient had received repeated doses of adrenaline, 11 ampoules in total, 13 litres of clear replacement fluids, 5 litres of blood, 0.5 litres of thrombocytes and 1 litre of fresh frozen plasma.

When the patient was transferred to a ward after 5 days of intensive care, the insulin mixtures hitherto used by her were changed to protamine-free preparations in the form of multi-injection treatment: 10+10+10 IU of protamine-free short-acting insulin (biosynthetic, human) and 20 IU of long-acting protamine-free zinc-human insulin-suspension (of recombinant DNA origin) administered at night. Treatment with insulin-glargine was also planned for the patient but there was no time to carry it out due to difficulties with the supply of the product. Skin grafts were performed on the lesions, and the patient left the hospital about two months from the date of arrival. The patient suffered a fatal acute extensive myocardiac infarction about two weeks later.

Since the reaction was exceptionally strong, previous indications of allergy were investigated following the episode. The patient did not exhibit any indicative signs and was unable to tell of any, so the situation came as a surprise to everyone involved. It was not until after the adverse effect that the patient remembered there having been complications with the use of insulins. The diabetes outpatient department also had a mention in their records of 1984 of the development of extensive itchy blisters, which were not caused by needle injections alone. Brands of insulin had been changed repeatedly through the years until the appropriate insulin mixture was found which did not cause a blister reaction.

Hypersensitivity reactions – how common are they?

Hypersensitivity reactions associated with surgical procedures are rare, despite the fact that a patient usually receives several different medicinal substances over a short period of time. In different reports, the number of reactions has been estimated at 5–250 per 100,000 anaesthesias administered (Langerh et al. 1982, Fisher et al. 1984), and the rate of mortality has been estimated at 4–6% (Langerh et al. 1982, Charpin et al. 1988). The reactions may nevertheless be serious and caused by allergy. The patients may later face new procedures, and to avoid risks, previous reactions and their causes ought to be investigated. In our case, the cause was evident – or, was it, after all? The patient had avoided fish and shellfish due to their taste, but no allergy to them had been detected. The patient had not been found to have significant resistance to insulin, and her diabetic treatment balance was good. The protamine-RAST measured about a month after the incidence was rather low, 0.6 IU/litre and S-IgE was previously normal. As the patient died soon after her stay in the ward, final confirmation could not be carried out. On the basis of this information, however, the reaction would have best fitted in with a strong anaphylactoid reaction, whereas reactions at the injection site and the rapid onset of the reaction would support a type I reaction.

How is a diagnosis arrived at?

Anaphylaxis is defined as a sudden, serious IgE-mediated hypersensitivity reaction, the symptoms of which appear within a couple of minutes; whereas an anaphylactoid reaction is independent of specific sensitisation and its symptoms are dependent on several transmitters released from the mast cells without antibody reactions. To distinguish an anaphylactic and an anaphylactoid reaction from each other at the time of occurrence is practically impossible, but later allergological examinations aim to establish the reaction in question.

Tests aimed at predicting life-threatening reactions have not been developed as yet, and the patient's medical history remains the only way of obtaining information beforehand. The decision remains with the anaesthetist and the surgeon on whether heparin replacements should be given, or whether the natural metabolism of heparin should be awaited. Special care is nevertheless recommended in the treatment of diabetics, and it is advisable that investigation of prota-

mine allergy should be considered before extensive vascular surgery.

What should be done if protamine allergy is detected?

Avoidance is one alternative – by using non-protamine insulins, a couple of which are available on the market – insulin-glargine would be the most appropriate choice among the long-acting insulins in multiinjection treatment. Reduced anticoagulation in surgery is not always feasible, e.g. in vascular surgery. Hence, heparin removal devices and various heparin removal filters etc. have been developed (von Segesser et al. 2001, Jegger et al. 2000). Common to all of them is their high price and the lack of experience. The most modern treatment alternatives tried include anti-TNF-α-antibodies which prevent the protamine-induced release of TNF-α and therefore also the cardiotoxicity of protamine (Pevni et al. 2001). As one alternative, heparin-degrading heparinase I has already progressed to phase 3 studies (Heres et al. 2001). Low-molecular protamine is also a promising subject of study (Tsui et al. 2001). Alternatives used e.g. in the treatment of patients with antibody-mediated heparin thrombocytopenia, such as lepirudin, danaparoid, tirofibane, iloprost and epoprostenol, all of them worthily discussed elsewhere (von Segesser et al. 2001), may be considered, based on the judgement of the anaesthetist and the surgeon. However, serious anaphylactic reactions to lepirudin have been reported. If time allows, the least complicated approach would seem to be to wait for the heparin to be metabolised normally: the most common plasma half-life is 90 ± 30 min (depending on the dosage – it is prolonged as the dose is increased). It should be borne in mind that the time span with heparin derivatives is considerably longer than with heparin.

Conclusion

All serious reactions should be reported to the ADR register including also those with known causes.

Accidentally developed sensitisation to protamine in insulin tolerance treatment should be borne in mind, albeit the cases are rare. In outpatient care it is also important to take note of injection site reactions in diabetics on insulin therapy. If reactions occur and vascular surgery is planned, it is recommended that allergy tests be carried out to examine the type of the reactions, or that information on the suspected allergy be included in the patient referrals. If operations are necessary, heparin substitutes could be used, for example, to avoid rare but even more complicated reactions.

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Reports on adverse drug reactions – who sends them?

Reports on suspected adverse drug reactions (ADR) are an important part of pharmacovigilance. The reports offer information on severe and unexpected adverse reactions, which are not detected in clinical trials (1).

In many countries pharmacists play an important role in the reporting of suspected adverse reactions. The National Agency for Medicines in Finland is often asked why pharmacists are not allowed to report adverse reactions. This study concentrates on the difference in practice that prevails regarding the ADR reports submitted by pharmacists and doctors. Would it change anything if the pharmacy personnel were given the right to report ADRs? For this study I made a comparison of reports submitted by people with pharmaceutical training and by medical doctors in the Netherlands during 1995–2000.

In this study, "people with pharmaceutical training" refers to people with a higher academic qualification in the Netherlands. A 6-year Diploma in Pharmacy in the Netherlands corresponds to the MPharm degree in Finland. For the sake of clarity, the term MPharm is used here.

In Finland, ADR reports are submitted by doctors and dentists to the ADR register of the National Agency for Medicine (2). The Netherlands Pharmacovigilance Foundation, or Lareb, maintains the ADR register in the Netherlands. Since 1984 MPharms have reported suspected adverse reactions to Lareb. They also play a kind of mediating role in the reporting of ADRs by the doctors (3).

The study aimed at reviewing the possible differences between the reporting practice of MPharms and medical doctors. I investigated the type of adverse reactions both groups reported, the drugs involved and the proportion of serious adverse reactions.

Material and methods

The study material consisted of the information reported to the register of Lareb. A single report could contain details of several different drugs, which were suspected of having caused an adverse reaction. The number of reports received was therefore smaller than the number of drugs involved. The seriousness of the ADRs is report specific, and therefore, if a report contained even one serious reaction, all the adverse reactions in that report were classified as serious.

The following information was collected from the reports: the number and year of the report, the ATC Code (4) and name of the drug, the suspected medicinal substance, the adverse reaction with a description, the extent of the reaction (severe or not severe), and the reporter (doctor or MPharm). The seriousness of the reactions was displayed in parallel in order to draw comparisons among the reporting groups. The crossproduct relationships and confidence intervals were calculated as a measure of their concordance.

Results

During the study period, the number of reports submitted by MPharms was smaller than that by doctors. Annually, about 40% of all the ADR reports are filled in by MPharms and about 60% by doctors (Table and Fig. 1).

ADR Reports

The ADR reports differed with regard to psychiatric adverse reactions: their share of all ADRs in 1996 totalled 6% of all reports by MPharms, whereas their share in the reports by doctors was about 11%. The number of reports submitted by

The number of ADR reports per reporting group in the Netherlands

	MsPharms		Doctors	
	n	*%*	*n*	*%*
1995	*887*	*37,5*	*1 481*	*62,5*
1996	*1 408*	*46,3*	*1 634*	*53,7*
1997	*1 627*	*44,9*	*2 000*	*55,1*
1998	*1 437*	*44,5*	*1 794*	*55,5*
1999	*1 315*	*41,6*	*1 843*	*58,4*
2000	*1 218*	*41,6*	*1 713*	*58,4*
Total/mean	***7 892***	***43,0***	***10 465***	***57,0***

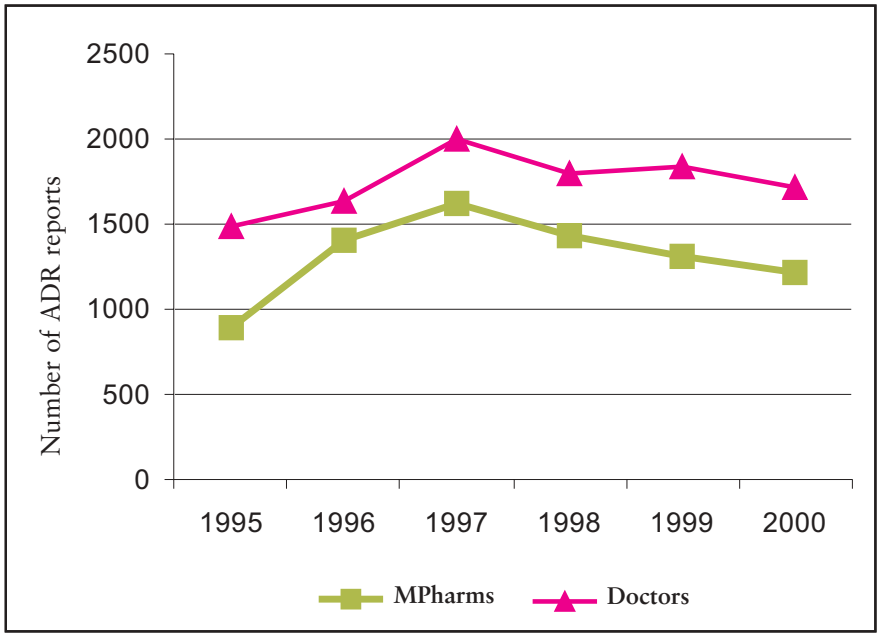

Fig. 1. The number of ADR reports per reporting group in the Netherlands

both groups remained approximately the same in 1997 (5% by MPharms and 12% by doctors). The difference became smaller later on: in 2000, the share of psychiatric adverse reactions among the reports submitted by MPharms amounting to about 6%, and those by doctors to about 8%. Dermatological adverse reactions and reactions relating to the subcutaneous tissue were reported more often by MPharms than by doctors. In 1997 their number among the reports given by MPharms was about a fifth, whereas they were involved in about every seventh report made by doctors. The difference remained the same in later years (1998–2000).

Drugs involved in the ADR reports

In 1995 there were only slight differences between the drugs reported by MPharms and those by doctors. From 1996 to 1999 there were significant differences between two groups of medical substances: cardiovascular drugs (ATC Code C) and antiparasitic products, insecticides and repellants (ATC Code P). Code P includes e.g. mefloquine, an antimalarial. Serious CNS adverse reactions caused by mefloquine were widely discussed in the media and professional journals during 1996–1997. As a result of this the reports of adverse reactions to mefloquine increased rapidly during those years.

MPharms reported more ADRs associated with cardiovascular drugs than doctors did, whereas doctors reported more reactions associated with antiparasitic products, insecticides and repellants than did the MPharms. Every fourth ADR report submitted by MPharms in 1996 involved cardiovascular drugs, whereas the corresponding figure for doctors was every sixth. ADRs associated with the use of antiparasitic products, insecticides and repellants were reported in a contrary way; they accounted for only about 4% of the reports by MPharms, whereas the corresponding figure for doctors was about 18%. In 1997 the difference was even bigger: 3% versus 23%.

Seriousness of the ADRs

The differences between the reporting practices of MPharms and doctors in relation to severe ADRs increased between 1995 and 2000. In 1995 MPharms and doctors reported an approximately equal number of severe ADRs, but in 2000 about 9% of all reports by MPharms and about 23% of all reports by doctors were associated with severe adverse reactions (Fig. 2). Statistically, the difference was significant every year after 1995.

Conclusion

Fewer ADRs in general were reported by MPharms than by doctors, which may be due to the fact that MPharms are fewer in number than are doctors. MPharms also reported fewer severe ADRs compared with doctors.

There were also differences between the ADRs reported by the two groups. It may be explained by the assumption that patients suffering from psychiatric adverse reactions will perhaps prefer to discuss them t with their doctors. Such reactions are usually related to prescription drugs, in which case the patient already has an established relationship with the doctor. Dermatological complications are easier to talk about in the pharmacy.

According to previous studies, there are two kinds of beliefs on how the reporting of serious ADRs is shared between the MPharms and the doctors. On one hand, a study carried out on hospital doctors and MPharms revealed that MPharms are more frequently inclined to report serious ADRs than doctors are (5, 6). On the other hand, according to a recent Dutch study, doctors were the ones who reported more frequent serious ADRs (3) in exactly the same way as this study shows.

In the Netherlands only less than 1% of all reports by MPharms originate from hospitals. Consequently, efforts are made by Lareb to encourage hospital MPharms to make more frequent reports.

Even though the participation of personnel with pharmaceutical training in the reporting of ADRs should be studied worldwide, the general opinion is that all countries should accept reports from them as well. Several studies have concluded that people with pharmaceutical training play an active part in the ADR monitoring (6).

It is not, however, always as straightforward as that. The most important reason for pharmacists and MPharms in Finland being unable to give reports on adverse reactions of drugs is based on the general principles of the drug supervisory authorities. Limited resources are considered better utilised when the ADR reporting is concentrated on serious ADR reports mainly from

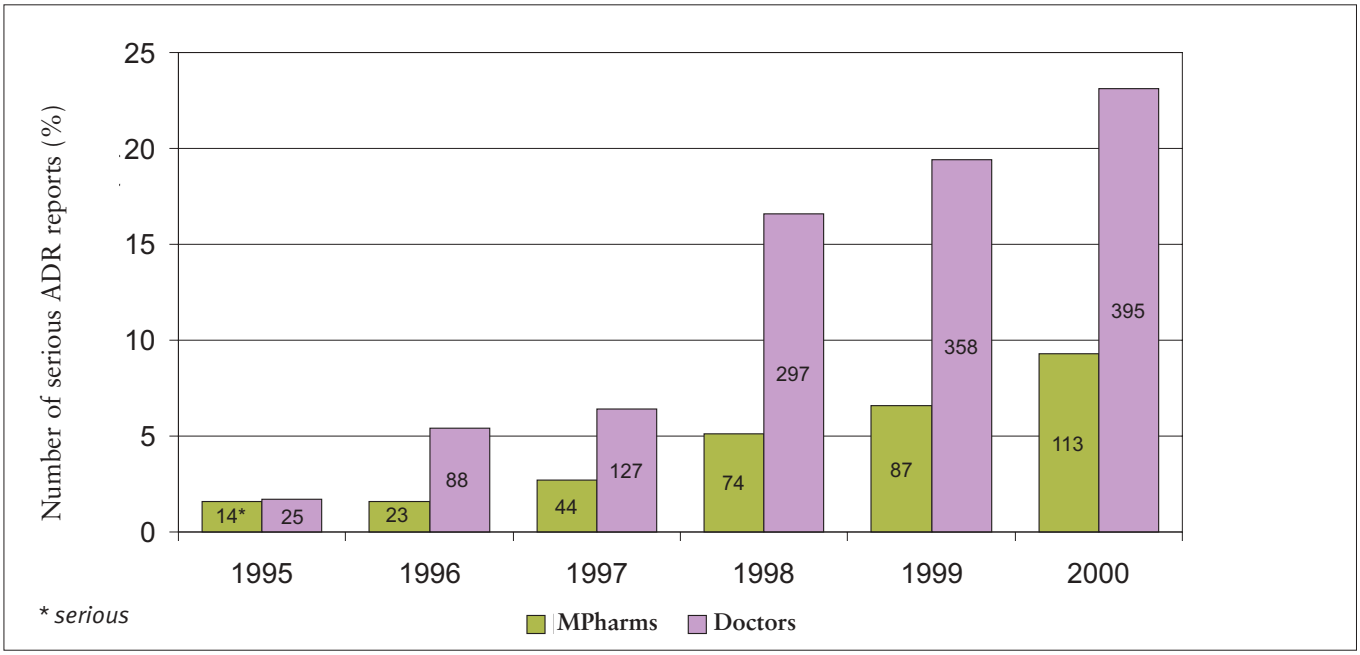

Fig. 2. The proportion of serious ADR reports per reporting group in the Netherlands

medical doctors. In any case, if a patient is suffering from a serious adverse reaction he/she is likely to contact a doctor. Consequently, the adverse reactions reported to the pharmacy would not, in the main, be serious ones, but ones previously known. Receiving a great number of reports of this type is probably unlikely to be useful, since the purpose of ADR reports is to obtain new or important information on drug safety. Should there be the intention to include pharmacy personnel in the reporting practice of ADRs, it needs first of all to be established how and to what extent it would be possible to carry this out sensibly, and what is aimed at in achieving it.

As ADR reporting is voluntary, the pharmacy personnel would need time to become familiar with the routine, and consequently, the use of resources available at pharmacies should be considered. Patient records are often required as enclosures to ADR reports. In a regular pharmacy this may be complicated and time-consuming and require contact with the patient's doctor. Hospital pharmacies may perhaps be more appropriate locations for training pharmacy personnel in the monitoring of adverse reactions and submitting of reports. A doctor would then be available if necessary, and monitoring of the patient's condition would be easier than in a regular pharmacy. At the same time, use could be made of the developing sector of pharmacy facilities available on the wards.

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