5.2001

IHBU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA
LÄKEMEDELSINFORMATION FRÅN LÄKEMEDELSVERKET, FINLAND | DRUG INFORMATION FROM THE NATIONAL AGENCY FOR MEDICINES, FINLAND

5.2001

9. vuosikerta
9 årgången
9th Annual volume

Sammandrag

Summary

Summary

Katja Lindgren-Äimänen
COMMUNICATIONS OFFICER, MSc (Pol)
Department of General Affairs

Ulla Närhi
Senior Pharmaceutical Officer, PhD (Pharm)
Drug Information Centre

National Agency for Medicines

Editorial

Information on medicine consumption available to everyone

Information on medicines and medicine consumption is widely needed in society. There is a demand especially for unbiased and objective information, which the National Agency for Medicines has at its disposal. Collecting the latest information on the sales and consumption of medicines, and knowing the current trends in the pharmaceutical field, are closely linked with monitoring the safety of medicines.

The National Agency for Medicines wants to provide the latest information on medicines more openly than before. Openness, flexibility, interactivity and activity in communications are also part of the government communication policy, as recommended last spring by the Working Group on Governmental Communication in the 2000s.

In October, the National Agency for Medicines will start publishing on Internet pages (**www.nam.fi**) medicine consumption statistics based on the data in the Register of Medicine Sales. Annual medicine consumption statistics have been published since 1987 jointly by the National Agency for Medicines and the Social Insurance Institution under the title Finnish Statistics on Medicines. The electronic version of consumption figures for the year 2000 will complement the printed volume. Both versions will be published in October.

The data in the Register of Medicine Sales is based on the monthly sales figures reported by pharmaceutical wholesalers. The medicine consumption by each therapy group is monitored on the basis of this data. Medicine consumption is expressed in terms of defined daily doses (DDD/1,000 inh. /day). Defined daily dose is an internationally used term for the consumption of medicines, where the quantities of medicines sold are converted to a figure expressing the defined daily dose relative to 1,000 inhabitants per the total population per day. Medicines are categorised according to the anatomic-therapeutic-chemical (ATC) classification system.

At first, the medicine consumption statistics published on the Internet will be the same as those published in the printed format. The charts will include the annual statistics for 1999 and 2000. Medicine consumption statistics will also be represented graphically based on selected charts.

In the future, our objective is to develop a user-friendlier package by facilitating the search for information further. When compiling statistics, we can also make use of regional consumption figures, and data on medicine consumption in earlier years. By monitoring the medicine sales patterns, we can draw conclusions on changes in medicine prescription practices and assess the rationale behind such changes. We would welcome any feedback on the publication of medicine consumption statistics, and suggestions for improvement. Please send your suggestions by e-mail to: **salesstatistics@nam.fi**.

The rearranging of the National Agency for Medicines' web site has begun. In the course of the autumn we will classify the web pages according to various interest groups, and create information service packages catering for their needs. We can then use this active communications channel as a medium for publishing news and current affairs. In the future, we plan to supply even more information on medicines and on the activities of the National Agency for Medicines on our renewed web site.

The Scandinavian countries supply similar data on medicine consumption at the following Internet addresses:

Denmark: ***http://www.dkma.dk***

Iceland: ***http://brunnur.stjr.is/interpro/htr/htr.nsf/pages/lyfjanotkun-1989-1999***

Finland: ***http://www.nam.fi***

Norway: ***http://www.drugconsumption.nmd.no***

Sweden: ***http://www.apoteket.se***

Translation Liisa Fellman-Paul

Summary

Hannu Koponen
PROFESSOR
Department of Psychiatry
University of Oulu

CHIEF PHYSICIAN
Hospital District of Lapland

Antidepressants used in anxiety disorders

Anxiety disorders are common psychiatric disorders often of long duration, with a significant effect on the patient's ability to function and the quality of life of the sufferers. They are also associated with a considerable risk of concurrent illnesses such as severe depression and drug/alcohol abuse. During the last decade, a lot of new information which can be applied in clinical practice has emerged regarding the medical treatment of anxiety disorders. The following survey discusses the biological background of anxiety disorders and the possibilities of medical treatment of panic disorders, social phobia, obsessive-compulsive disorders and generalised anxiety disorders.

Normal anxiety signals a threat and serves as encouragement to a person to cope with the impending situation on his/her own. Anxiety also promotes the feeling of togetherness and improves emotional ties between individuals, thereby helping the community to cope better. Anxiety may be considered exceptional if its duration or degree of severity is unbalanced in relation to the threat causing the anxiety or if the anxiety occurs without a triggering factor. Anxiety disorders (Table 1) are the commonest of the psychiatric disorders, occurring in at least 7–10% of Finns according to earlier reports (Lehtinen et al. 1990), though even higher frequencies of over 15% in western countries have been reported (e.g. Kessler at al. 1994). Anxiety disorders are associated with a significant reduction in ability to function, reduced ability to work and concurrent illnesses such as depression.

Causes of exceptional anxiety have been thought to consist of internal mental conflicts, unusual conditioning, or disturbances in the cognitive treatment of emotional states. According to recent studies, besides factors associated with the growing environment, genetic factors also play a role (Kendler et al. 2001). From the point of view of neurobiology, anxiety is a state which is developed jointly through the brainstem, the limbic system, prefrontal areas of the cerebral cortex and the cerebellum. The nuclei of the brainstem, e.g. the locus coeruleus, take part in the control of alertness, whereas the limbic system controls the physiological and emotional responses associated with the threat factors. The hippocampus and amygdala also play an important role in the control of the content of memory associated with emotional states. The prefrontal areas control the management of action and decisionmaking. These functions are mediated via several neurotransmitters such as gamma-aminobutyric acid, noradrenaline, serotonin and corticotropin-releasing hormone, which offers the opportunity for medical interference with the activity of nerve networks important in the development of anxiety disorders (Noyes and Hoehn-Saric 1998).

Table 1. ***Neurotic somatoform disorders associated with stress*** *(Disease classification ICD-10 1997)*

- *phobic anxiety disorders*
  - *agoraphobia*
  - *social phobia*
  - *defined (individual) fears*
- *other anxiety disorders*
  - *panic disorder*
  - *generalised anxiety disorder*
  - *mixed anxiety disorder and depression*
  - *obsessive-compulsive disorder*

The serotonin pathways start from a nucleus in the median raphe of the medulla and continues to the limbic and nigrostriatal area and the cerebral cortex. At least 14 different serotonin receptors have been detected with certainty, and consequently the effects of the serotonergic network on anxiety are varied and partly also conflicting. The serotonin system reduces the prefrontal cerebral cortex activity and stabilises alertness by its effect on the locus coeruleus. These effects reduce anxiety and explain the anxiety-removing effect of drugs with an influence on the serotonin system (Shelton and Brown 2001). Antidepressants may also have beneficial neuroprotective effects (Raid and Stewart 2001).

Anti-anxiety drugs

Ethanol, bromides, paraldehyde, barbiturates and meprobamate have previously been used for anxiety and sleep disturbances with varied success. Their use was, however, associated with considerable problems of dosage, toxic effects and drug dependence, and consequently the benzodiazepines developed at the end of the 1950s rapidly attained an important position in the treatment of anxiety disorders. In some patients, and es-

pecially on long-term use, they are, however, associated with problems of dependence, tolerance and the necessity of increasing the dose; which is why other psychotropic drugs (traditional antipsychotics and tricyclic antidepressants previously, and more recent antidepressants to an increasing degree since the beginning of the 1990s) have been used in long-term treatment of anxiety disorders (Lepola 1999). New groups of drugs to treat anxiety disorders are also under development which, in their mechanism of action, differ from the foregoing.

Antidepressants in anxiety disorders

Among antidepressants imipramine, for instance, has been used since as early as the 1960s in long-term treatment of anxiety disorders such as panic disorder. However, antidepressants mainly affecting the serotonergic activity and introduced on to the market at the turn of the decade of 1980/1990 and new two-channel antidepressants introduced into use after the mid 1990s, have widened their use in the treatment of anxiety disorders, partly due to the improved tolerability of new molecules.

The efficacy of antidepressants is based on their regular use and it may take several months until any response emerges (Table 2). When antidepressants are used to treat anxiety disorders, the treatment should usually be started with a small initial dose and the dose should thereafter be increased slowly to avoid adverse effects in the initial stages. The therapeutic doses used are nevertheless similar to those used in the treatment of depression (Leinonen et al. 2000). Treatment of anxiety disorders is often long-term, but there are very few studies of the time scales used in the treatment. Clinical experience has shown, however, that a minimum 6–12 months of treatment is required in most anxiety disorders. Adverse effects associated with the use of antidepressants, the most common of which are initial nausea, and sexual adverse effects and increased sweating on longer term use, have not usually obstructed the treatment, and this is especially important in disorders requiring long-term treatment. Towards the end of the medical treatment, gradual withdrawal of medication is often advisable (Michelson et al. 2000).

Generalised anxiety

The important symptoms of generalised anxiety include anxiety, excessive care and various somatic symptoms associated with these. Its lifelong prevalence is on average 5–6% and it is often associated with other concurrent psychiatric disturbances such as depression and drug abuse. As a disturbance of long duration, it usually has a significant adverse effect on the ability to function. The number of drug trials in generalised anxiety is smaller than that in other anxiety disorders, but in studies with paroxetine and venlafaxine, for instance, the initial signs of the effect of treatment have been visible within 2–3 weeks and the response has improved with higher doses (Allgulander et al. 2001).

Panic disorder

Panic disorder is characterised by severe mental attacks of anxiety which, besides various somatic symptoms, are also associated with a fear of death or a fear of losing control and becoming insane. Panic disorders may occur spontaneously or they may be associated with various situations. The life-long prevalence of panic disorders is estimated at about 3% (Academy of Finland 2000). They are also associated with a considerable risk of depression when the patient's symptoms worsen, and concurrent depression is also associated with a higher risk of suicide and a more severe reduction in the quality of life (Roy-Byrne et al. 2000).

Previously, panic disorders were often treated with benzodiazepines, but the primary medical treatment for panic disorders nowadays consists of selective serotonin re-uptake inhibitors. The efficacy of all serotonin selective antidepressants in use

Table 2. ***A comparison of properties of benzodiazepines, buspirone and antidepressants.***

	Benzodiazepines	*Buspirone*	*Antidepressants*
Single dose is effective	*Yes*	*Yes*	*No*
Time before the start of complete response	*Days*	*Weeks*	*Weeks*
Tiredness	*Yes*	*No*	*No*
Risk of dependence	*Yes*	*No*	*No*
Impairs performance	*Yes*	*No*	*No*
Decreases withdrawal symptoms	*Yes*	*No*	*No*
Dosage once a day	*No*	*No*	*Yes*
Efficacy in concurrent depression	*No*	*No*	*Yes*
Most common adverse effects	*Tiredness, memory disturbances*	*Anxiety, nervousness*	*Gastrointestinal symptoms, disturbances of sexual function*

in Finland is documented in the treatment of panic disorders. Initially, a small dose should be used which is then increased to the therapeutic dose within a couple of weeks. A response to treatment is usually obtained within 3–6 weeks of treatment and the treatment should be continued for at least 6–12 months after recovery (Lepola et al. 1998).

Social phobia

Social phobia is the most common anxiety disorder occurring in the general public. Epidemiological studies have found its prevalence to be around 4–8%, and symptoms occurring in most situations associated with performance and interaction have an especially significant adverse effect on education, work and quality of life (Stein et al. 2000). New antidepressants and behavioural therapy are also beneficial in the treatment of social phobia, and the combined use of these forms of treatment is recommended at least for the most severe symptoms (Blomhoff et al. 2001). The use of antidepressants in long-term treatment of social phobia is also supported by the risk of depression associated with this disorder. Bouts of depression occur in about a half of these patients, and social phobia in adolescents or young adults is considered to be a risk factor for bouts of depression later in life (Stein et al. 2001).

Obsessive-compulsive disorder

Obsessive-compulsive disorder was previously considered rare, but epidemiological studies have changed the estimate of its prevalence because 1–2.5% of the adult population suffers from this type of anxiety disorder. Even though few people recover totally with treatment, the aim of treatment is to diminish the occurrence of symptoms and adverse effects on the daily life. The symptoms of patients who benefit from treatment are usually reduced by 30–70%, and the treatment of patients with a positive response should be continued for at least one year, often even longer. A significant risk of depression is associated with obsessive-compulsive disorder, and about 60% of patients suffer from severe depression at some stage of their lives. Antidepressants based on serotonin re-uptake inhibition are effective in the treatment of obsessive-compulsive disorder, and the doses used are often at the upper end of the dosage scale (Koponen et al. 1997). Patients with obsessive-compulsive disorder do not, however, benefit from benzodiazepines or antipsychotics. Antidepressants are an effective alternative also for patients who suffer from depression in addition to obsessive-compulsive disorder (Hoehn-Saric et al. 2000).

Conclusion

Anxiety disorders are common and they are associated with significant adverse effects in the form of subjective suffering, reduced capacity for work and other concurrent disabilities. For the treatment of anxiety disorders of long duration, the aim has been to develop forms of treatment with improved tolerability and without associated dependence-forming tendencies, examples of which are the use of serotoninselective and new two-channel antidepressants in different anxiety disorders. In the treatment of anxiety of short duration, benzodiazepines still offer the most commonly used choice of medical treatment, even though drugs with similar effects but without the associated adverse effects are continuously being developed.

Literature

Academy of Finland: Paniikkihäiriö. Konsensuslausuma. Vammalan kirjapaino, Vammala 2000.

Allgulander C, Hackett D, Salinas E: Venlafaxine extended release (ER) in the treatment of generalized anxiety disorder. Br J Psychiatry 2001;179:15-22.

Blomhoff S, Haug TT, Hellström K, Holme I, Humble M, Madsbu HP, Wold JE: Randomized controlled general practice trial of sertraline, exposure therapy and combined treatment in generalized social phobia. Br J Psychiatry 2001;179:23-30.

Disease classification ICD-10. Psykiatriaan liittyvät diagnoosit. Stakes, Rauma 1997.

Hoehn-Saric R, Ninan P, Black DW, Stahl S, Greist JH, Lydiard B, McElroy S, Zajacka J, Chapman D, Clary C, Harrison W: Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. Arch Gen Psychiatry 2000;57:76-82.

Kendler KS, Myers J, Prescott CA, Neale MC: The genetic epidemiology of irrational fears and phobias in man. Arch Gen Psychiatry 2001;58:257-265.

Kessler RA, McGonacle KA, Zhao S ym: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 1994;51:8-19.

Koponen HJ, Lepola U, Leinonen E, Jokinen R, Penttinen J, Turtonen J: Citalopram in the treatment of obsessive-compulsive disorder. An open pilot study. Acta Psychiatr Scand 1997:96:343-346

Lehtinen V, Joukamaa M, Lahtela K, ym. Prevalence of mental disorders among adults in Finland: Basic results from Mini Finland Health Survey. Acta Psychiatr Scand 1990;81:418-425.

Leinonen E, Lepola U, Koponen H: Ahdistuneisuuden lääkehoito. Duodecim 2000;116:2855-2864.

Lepola UM, Wade AG, Leinonen EV, Koponen HJ, Frazer J, Sjödin I, Penttinen JT, Pedersen T, Lehto HJ: A controlled prospective 1-year trial of citalopram in treatment of panic disorder. J Clin Psychiatry 1998;59:528-534.

Lepola U: Ahdistuneisuuden lääkehoidon kehitys. Kirjassa Kähkönen S, Partonen T: Mielen lääkkeet - lääkkeen mieli. Duodecim, Helsinki 1999.

Michelson D, Fava M, Amsterdam J, Apter J, Londborg P, Tamura R, Tepner RG: Interruption of selective serotonin reuptake inhibitor treatment. Br J Psychiatry 2000;176:363-368.

Noyes R, Hoehn-Saric R: The anxiety disorders. Cambridge University Press, Cambridge 1998.

Raid IC, Stewart CA: How antidepressants work. New perspectives on the pathophysiology of depressive disorder. Br J Psychiatry 2001;178:299-303.

Roy-Byrne PP; Stang P, Wittchen H-U, Ustuin B, Walters EE, Kessler RC: Lifetime panic-depresion comorbidity in National Comorbidity Survey. Br J Psychiatry 2000;176:229-235.

Shelton RC, Brown LL: Mechanisms of action in the treatment of anxiety. J Clin Psychiatry 2001; 62(suppl 12):10-15.

Stein MB, Torgrud LJ, Walker JR: Social phobia symptoms, subtypes and severity. Arch Gen Psychiatry 2000;57:1046-1052.

Stein MB, Fuetsch M, Muller N, Höfler M, Lieb R, Wittchen H-U: Social anxiety disorder and the risk of depression. Arch Gen Psychiatry 2001;58:251-256.

Summary

Hellevi Ruokonen
Specialist in Clinical Dentistry, Ph.D, MSc
Department of Oral and Maxillofacial Diseases
Surgical Hospital
Helsinki and Uusimaa Hospital Group

Drugs and gingival overgrowth

Two of the most important drugs with gingival overgrowth (gingival hyperplasia) are ciclosporin (1), and calcium channel blockers (2,3). Phenytoin has also been reported to have caused gingival overgrowth (4), (Table). Phenytoin-induced gingival overgrowth is, however, seen by a dentist less frequently nowadays as other drugs are also used for the treatment of epilepsy today.

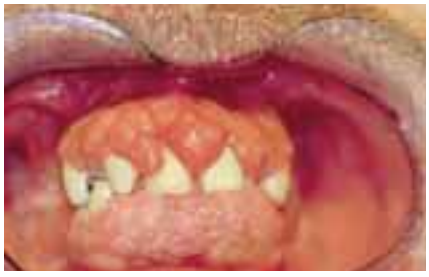
The term gingival hyperplasia has been used hitherto in the literature for gingival overgrowth. Gingival hyperplasia denotes a condition where the number of cells in the tissue is increased. From a histological point of view, the number of fibroblasts in drug-induced gingival overgrowth is not increased significantly, but the amount of collagen and intercellular material produced by them is, probably due to the reduced rate of metabolism (5,6). Consequently, the English literature nowadays most often uses the term gingival overgrowth or gingival enlargement rather than gingival hyperplasia.

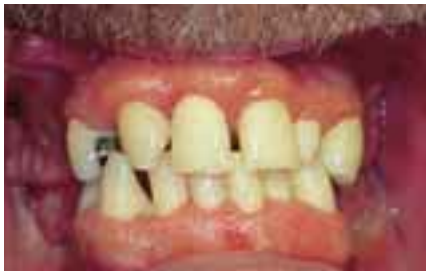
Gingival overgrowth hinders the daily cleaning of the teeth and causes plaque accumulation, and may thereby perpetuate gingivitis. On the other hand, the development of overgrowth is encouraged by gingivitis associated with poor oral hygiene or by periodontitis, an infection which has advanced further to the periodontium of the teeth. Gingival overgrowth often starts in the interdental spaces and is usually more prominent on the labial surfaces of the teeth than on the palatal or lingual surfaces. In severe cases the overgrowth is generalised in the entire dental area and may be extended as far as the occlusal surface of the teeth, interfering with chewing (Fig. 1 a and b). Gingival overgrowth is often a functional as well as a cosmetic impediment. In association with ciclosporine, the possible development of malignancies should also be considered; squamous cell carcinoma and Kaposi's sarcoma have been reported in the literature (7,8). Overgrowth should consequently be removed surgically and a tissue sample taken for histological examination (9).

Drugs, which may cause gingival overgrowth

• *Ciclosporin*	*Sandimmun*
• *Calcium channel blockers*	
Diltiazem	*Cardizem, Dilmin, Dilpral, Dilzem, Viazem*
Verapramil	*Chronovera, Isoptin, Vermin, Verpacor, Verpamil*
Dihydropyridine derivatives	
- amlodipine	*Norvasc*
- felodipine	*Hydac, Plendil*
- isradipine	*Lomir*
- lercanidipine	*Zanidip*
- nifedipine	*Adalat, Nifangin, Nifdemin, Nifecor*
- nisoldipine	*Syscor*
- nilvadipine	*Escor*
• *Phenytoin*	*Hydantin*

Fig. 1 a and b. ***A heart transplant patient on combined ciclosporin and calcium channel blocker therapy.*** *The patient had pronounced gingival overgrowth which was surgically removed. a = prior to treatment, b = after treatment.*





Ciclosporin

Ciclosporin is an immunosuppressive agent which is used to prevent organ rejection in kidney, liver, heart, heart/lung, lung or pancreas transplantation. It is also used in bone marrow transplantations both for the prevention and treatment of graft-versus-host disease (GVHD). Other indications for ciclosporin include rheumatoid arthritis, nephrotic syndrome, endogenous uveitis, severe psoriasis and severe atopic dermatitis (10,11).

Ciclosporin is a cyclic polypeptide consisting of 11 amino acids. It prevents the development of cell-mediated reactions by inhibiting T-cell proliferation. At the cell level, ciclosporin prevents the generation and release of lymphokines, including interleukin-2. Ciclosporin inhibits T-

cell activation at the start of the cell cycle by preventing the release of lymphokines. It has a less important effect on B-cell activity and it does not interfere with haematopoiesis or influence the phagocyte activity (10, 12,13).

Gingival overgrowth was reported for the first time in the literature in 1983 (1). The prevalence of overgrowth in organ transplant patients varies considerably according to different studies (8%–70%), most likely due to the variety of patient groups (11,14). The prevalence in children has been reported to be as high as 80% (15,16). Fibrotic, thickened gums in children may prevent the normal eruption of permanent teeth (Fig. 2 a and b). There are no reports in the literature of overgrowth caused by ciclosporin in edentulous areas.

Overgrowth typically begins at the gingival papillae. Overgrown excessive tissue must often be removed surgically before maintenance of the patient's normal oral hygiene is even possible (Fig. 3 a and b).

Calcium channel blockers

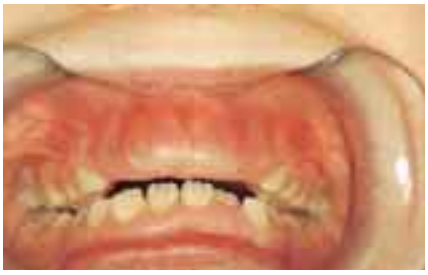
The first case of gingival overgrowth developed as an adverse effect of calcium channel blockers was associated with nifedipine and was reported in 1984 (2). Gingival overgrowth has also been reported of verapamil (3), amlodipine (17), felodipine (18) and diltiazem (19). Gingival overgrowth caused by calcium channel blockers is clinically similar to that caused by ciclosporine or phenytoin, see Fig. 4 a and b.

Calcium channel blockers are often used for the treatment of hypertension in kidney transplant patients. Kidney transplant patients receiving nifedipine in addition to ciclosporine have a higher risk of developing overgrowth (9,20). According to one study, the extent and severity of overgrowth is significantly related to the plasma concentration of ciclosporine (21).

Phenytoin

Gingival overgrowth caused by phenytoin was reported for the first time in medical literature over 60 years ago (4). Studies have shown a correlation between the gingival overgrowth caused by bacterial plaques and dental calculus and that caused by phenytoin (22,23). Gingival overgrowth typically starts from gingival papillae and is often localised to the area of the front teeth. Overgrowth can occur in the entire dental area. Overgrowth caused by phenytoin has also been reported in edentulous patients (24).

Fig. 2 a and b. ***A 7-year-old kidney transplant patient on ciclosporin therapy.*** *The gingival tissue in the upper front dental area is thickened by fibrosis, preventing the emergence of permanent teeth (a). The patient had a gingival operation under general anaesthesia, with exposure of the permanent upper front teeth. Fig. (b) 2 weeks after the procedure.*



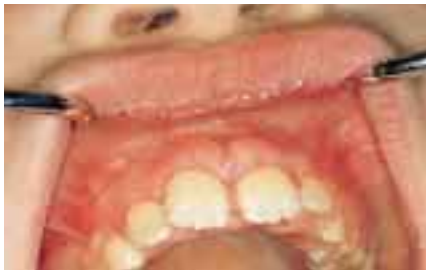
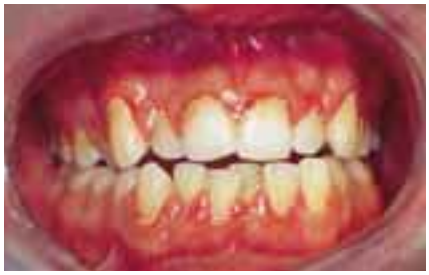


Fig. 3 a and b. ***A heart and kidney transplant patient on combined ciclosporin and calcium channel blocker therapy.*** *The marginal gingiva is infected and the gingival papillae have overgrown, preventing normal dental care at home (a). The overgrowth was removed surgically, dental calculus and bacterial films were removed, and the patient was advised on proper dental care at home. b = after treatment.*



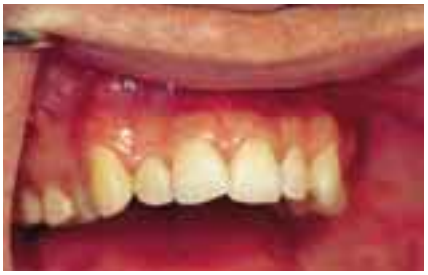
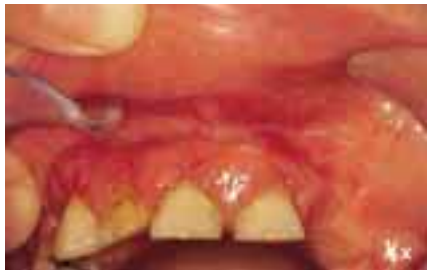
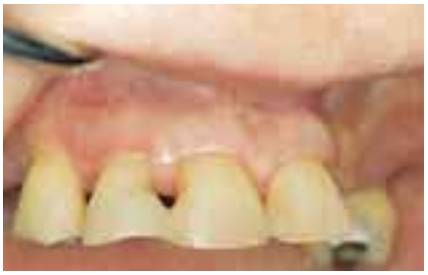


Fig. 4 a and b. ***The patient was on felodipine therapy with gingival overgrowth.*** *The patient also has periodontitis, an untreated infection of the periodontium. a = prior to treatment, b = after treatment.*





Treatment

Treatment of gingival overgrowth consists of its surgical removal. The overgrowth can be removed by gingivectomy or periodontal flap surgery (25). In gingivectomy, the surface of the wound is often treated with a CO_2 laser. The benefits of the use of a CO_2 laser are: good haemostasis, reduced postoperative pain and swelling, and a sterilising effect on the wound surface. The patient should be provided with a total dental treatment plan which would include the extraction of teeth with poor prognosis and the planning of basic periodontal treatment with associated removal of overhanging margins of fillings and crowns and dental calculus and instruction of the patient in a correct dental cleaning technique. Changes caused by plaque-retaining caries should be treated with fillings. Prevention of overgrowth includes careful dental care at home and professional cleaning of teeth carried out by a dentist or a specialised den-

tal nurse, with maintenance treatment at individually determined intervals, which in some patients may be as frequently as every couple of months.

Transplant patients receiving ciclosporine therapy should be given antimicrobial prophylaxis in dental treatment procedures which cause haemorrhage. Furthermore, when antimicrobial treatment is planned for a patient on ciclosporines, possible interaction between the antibiotic and ciclosporine should be considered. Erythromycin, doxycycline and fluconazole, for example, increase the ciclosporin concentration in plasma.

Cases have been reported in the literature concerning the use of azithromycin for the treatment of ciclosporine-induced gingival overgrowth (26,27). Azithromycin is a macrolide antibiotic agent of the azalide group. The agent is strongly bound to the tissues ; pharmacokinetic studies have detected considerably higher concentrations in tissue than in the plasma. There are no studies, however, of the interactions of azithromycin and ciclosporine, and consequently the circumstances of treatment should be carefully considered before these drugs are used concurrently (10).

Summary

The pathogenesis of gingival overgrowth caused by ciclosporine, calcium channel blockers and phenytoin is not known. An interaction of several varying factors is likely. A common pointer for these drugs is that they have an inhibiting effect on the inflow of calcium ions into the cell membrane. Alternative drugs are often not possible. The only remaining alternative treatment is therefore surgical removal of the gingival overgrowth, treatment of the periodontium, and careful self-treatment at home, since the development of overgrowth is encouraged by plaque associated with poor oral hygiene and the consequent inflammatory changes.

Literature

1. Rateitchak-Plüss EM, Hefti A, Lörtscher R, Thiel G. Initial observation that cyclosporin-A induces gingival enlargement in man. J Clin Periodontol 1983; 10: 237-246.

2. Lederman D, Lumerman H, Reuben S, Freedman PD. Gingival hyperplasia associated with nifedipine therapy. Oral Surg 1984; 57: 620-622.

3. Mehta AV, Chidambaram B, O´Riordan AC. Verapamil-induced gingival hyperplasia in children. Am Hearth J 1992, 124: 535-536.

4. Kimball OP. The treatment of epilepsy with sodium diphenyl hydantoinate. JAMA 1939; 112: 1244-1245.

5. Lucas RM, Howell LP, Wall BA. Nifedipine-induced gingival hyperplasia. A histochemical and ultrastructural study. J Periodontol 1985; 56: 211-215.

6. Tipton DA, Fry HR, DabbouS MKh. Altered collagen metabolism in nifedipine-induced gignival overgrowth. J Periodontol Res 1994; 29: 401-409.

7. Varga E, Tyldesley WR. Carcinoma arising in cyclosporin-induced gignival hyperplasia. Br Dent J 1991; 171: 26-27

8. Qunibi WY, Akhtar M, Ginn E, Smith P. Kaposi´s sarcoma in cyclosporine-induced gingival hyperplasia. Am J Kidney Dis 1988; 11: 349-352.

9. Morgan JD; Swarbrick MJ, Edwards CM, Donnelly PK. Cyclosporin, nifedipine and gingival hyperplasia: a randomized controlled study. Transpl Int 1994; 7, Suppl 1:S320-321.

10. Pharmaca Fennica 2001; 1764-1767.

11. Rees TD, Levine RA. Systemic drugs as a risk factor for periodontal disease initiation and progression. Compendium 1995; 16: 20-42.

12. Borel JF. The history of cyclosporin A and its significance. In D.J.G.White (ed), Cyclosporine A (pp.5-17). New York 1982, Elsevier Biomedical.

13. Larsson EL. Cyclosporin A and dexamethasone suppress T cell response by selectively acting at distinct sites of the triggering process. J Immunol 1980; 128: 2828-2833.

14. Daley TD, Wysocki GP, Day C. Clinical and pharmacologic correlations in cyclosporine-induced gingival hyperplasia. Oral Surg Oral Med Oral Pathol 1986; 62: 417-421.

15. Allman SD, McWhorter AG, Seale NS. Evaluation of cyclosporine induced gingival overgrowth in the pediatric transplant patients. Pediatr Dent 1994; 16: 36-40.

16. Karpinia AK, Matt M, Fennell III SF, Hefti FA. Factors affecting cyclosporine-induced gingival overgrowth in pediatric renal transplant recipients. Pediatr Dent 1996; 18: 7: 450-455.

17. Seymour RA, Ellis JS, Thomason JM, Monkman S, Idle JR. Amlodipine-induced gingival overgrowth. J Clin Periodontol 1994; 21: 281-283.

18. Lombardi T, Fiore-Donno G, Belser U, DiFelice R. Felodipine-induced gingival hyperplasia: a clinical and histologic study. J Oral Pathol Med 1991; 20: 89-92.

19. Bullon P, Machuca G, M-Sahuquillo A. Clinical assessment of gingival size among patients treated with diltiazem. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 79: 300-304.

20. O´Valle F, Mesa F, Aneiros J, Gómez-Morales M, Lucena MA, Ramirez C, Revelles F, Moreno E, Navarro N, Caballero T, Masseroli M, Garcia del Moral R. Gingival overgrowth induced by nifedipine and cyclosporin A. Clinical and morphometric study with image analysis. J Clin Periodontol 1995; 22: 591-597.

21. Thomas DW, Baboolal K, Subramanian N, Newcombe RG. Cyclosporin A-induced gingival overgrowth is unrelated to allograft function in renal transplant recipients. J Clin Periodontol 2001; 28: 706-709.

22. Addy V, McElnay JC, Eyre DG, Campbell N, D'Arcy PF. Risk factors in phenytoin-induced gingival hyperplasia. J Periodontol 1983; 54: 373-377.

23. Penarrocha-Diago M, Bagan-Sebastian JV, Vera-Sempere F. Diphenylhydantoin-induced gingival overgrowth in man: A clinicopathological study. J Periodontol 1990; 61: 571-574.

24. Bredfeldt GW. Phenytoin-induced hyperplasia found in edentulous patients. J Am Dent Assoc 1992; 123: 61-64.

25. Pilloni A, Camargo PM, Carere M, Carranza FA Jr. Surgical treatment of cyclosporine A- and nifedipine-induced gingival enlargement: gingivectomy versus periodontal flap. J Periodontol 1998, 69: 791-797.

26. Nash MM & Zaltzman JS. Efficacy of azithromycin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant recipients. Transplantation 1998; 65(12): 1611-1615.

27. Nowicki M, Kokot F & Wiecek A. Partial regression of advanced cyclosporin-induced gingival hyperplasia after treatment with azithromycin. A case report. Ann Transplant 1998; 3: 25-27

Summary

Tinna Voipio
RESEARCHER
Drug Information Centre
National Agency for Medicines

Consumption of anti-inflammatory analgesics: the effect of the switch to OTC

Acetylsalicylic acid (ASA), numbers of combination preparations containing ASA, and paracetamol have traditionally been available in Finland without a prescription (over-the counter, OTC) for the treatment of pain and fever. More recent anti-inflammatory drugs, ibuprofen and ketoprofen, have later been included among these OTC drugs. The consumption of anti-inflammatory drugs has been widely discussed. OTC category has been expected to boost the sales of the preparation due, for instance, to improved availability and permitted marketing to the general public. A survey has been made of the effects that the switch to OTC drugs has had on the consumption of anti-inflammatory drugs (1). In this article the figures from the survey have been augmented with the sales figures for 2000. The target of the survey is the consumption of anti-inflammatory analgesics and paracetamol (DDD/1,000 inhabitants/day) during 1989–2000.

The range of anti-inflammatory analgesics

The range of anti-inflammatory analgesics available by prescription in 1989 consisted of 17 drugs and combinations of drugs. By the year 2000 only 13 of these remained in use, and 7 new drugs and 2 new combinations had been introduced on to the Finnish market through the years. The most recent additions to the selection are the COX-2 selective anti-inflammatory drugs.

The range of OTC drugs has been simplified in recent years. Anti-inflammatory drugs available nowadays include ketoprofen and dexibuprofen plain, and ASA, ibuprofen and paracetamol both plain or as combination preparations which also include active ingredients such as vitamin C, caffeine and/or an antitussive. In association with renewals of marketing authorisations for analgesics in 1998 it was considered that combination preparations consisting of one or more ASA derivatives or containing combinations of codeine and caffeine were no longer appropriate today in the light of their efficacy and safety, and their marketing authorisations were consequently no longer renewed.

Ibuprofen and ketoprofen as OTC drugs

The first OTC preparations of 200 mg ibuprofen in packages of 20 tablets were introduced on to the market in 1987, and 400 mg ibuprofen in 10-tablet packages was introduced in June 1989. Since OTC preparations are mainly intended for temporary use, the total amount of ibuprofen in OTC packages is restricted to 4 grams. No special safety risks have been reported from the subsequent OTC use of ibuprofen. In 2000, ibuprofen accounted for 55% of the retail sale value, and 59% of the consumption, of OTC analgesics.

The introduction of ketoprofen in an OTC status has been more complicated. Small packages of ketoprofen 50 mg (15 capsules and 10 tablets) were brought on to OTC market in September 1992. Discussions on the efficacy and safety of ketoprofen in large doses were started soon afterwards. As knowledge about the use improved, it emerged that, in many cases, a sufficient effect is reached with a single dose of as little as 25 mg, and that the efficacy is not significantly increased by further increases in dose. Increasing the dose nevertheless increases the adverse effects considerably (2). It was consequently considered inappropriate to retain the 50 mg strength among the OTC range. It was transferred back to the POM-category in July 1996, while small packages of 25 mg ketoprofen remained among the OTC drugs.

Total consumption of anti-inflammatory analgesics

The total consumption (DDD/1,000 inhabitants/day) of anti-inflammatory analgesics during the past 12 years has increased by 16% (OTC drugs by 3% and prescription drugs by 26%, Fig. 1). The increase has not been steady, but the consumption has both decreased and increased during the survey period.

Consumption of anti-inflammatory prescription drugs

The biggest changes have occurred in the consumption of ketoprofen and ibuprofen (Fig. 2). The consumption of ketoprofen peaked in 1994, totalling 11.86 DDD/1,000 inhabitants/day. The consumption has decreased since and totalled 5.07 DDD/inhabitants/day in 2000.

The increase in consumption of

ibuprofen occurred towards the end of the survey period. It is the most commonly used anti-inflammatory analgesic in Finland at present.

The consumption of naproxen increased steadily at the beginning of the survey period and peaked (9.12 DDD/1,000 inhabitants/day) in 1996, when it was the most commonly used anti-inflammatory analgesic. Its use has since gradually decreased.

The consumption of paracetamol has increased steadily since its modest start. The consumption of nimesulide, introduced on to the market in 1997, has increased sharply. Byt 2000 it was already the third most commonly used anti-inflammatory drug with consumption reaching 6.24 DDD/1,000 inhabitants/day.

The consumption of diclofenac has remained steady during the entire survey period. The consumption of tolfenamic acid, indometacin and piroxicam has decreased continuously.

Consumption of OTC drugs

The consumption of OTC drugs has increased by only 3% during the past 12 years, and there has been a concurrent switch in consumption from combination preparations to preparations consisting of only one active substance. The consumption of preparations containing one active substance has increased by 29% and the consumption of combination preparations has decreased by 65% (Fig. 3).

The biggest changes in the consumption of OTC preparations are found in the decreased consumption of combination preparations and ASA and in the increased consumption of ibuprofen (Fig. 4).

ASA used to be the most commonly used analgesic in self-medication. Its consumption has decreased continuously during the last ten years. The consumption of ASA (DDD/1,000 inhabitants/day) has decreased by 62% in 12 years. The decrease has been steady except for a rise which occurred in 1993.

The consumption of OTC preparations of ibuprofen has been constantly on the increase. In 1995, its consumption reached the level of that of ASA and since 1996 it has

Fig. 1. ***Total consumption of anti-inflammatory analgesics*** *(DDD/1,000 inhabitants/day).*

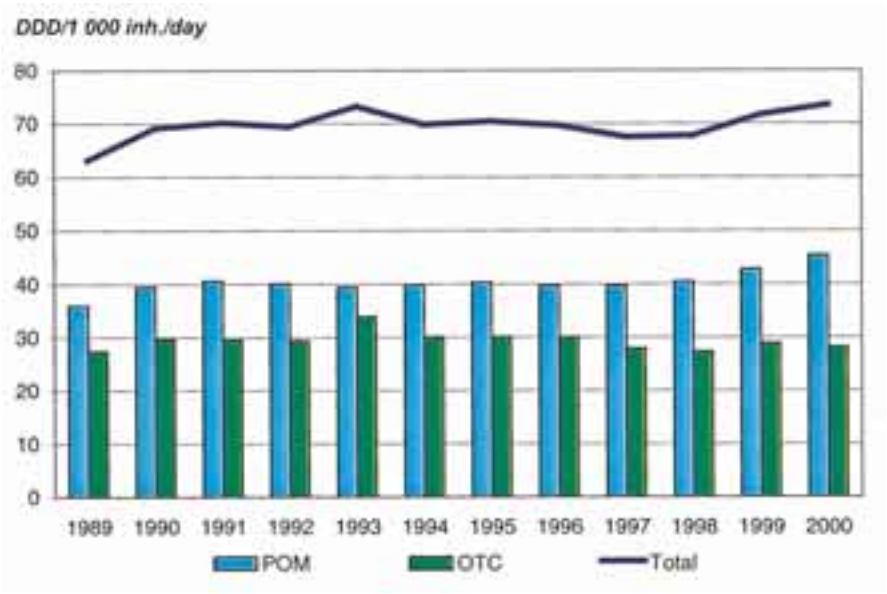


Fig. 2. ***Consumption of the most common anti-inflammatory prescription drugs*** *(DDD/1,000 inhabitants/day).*

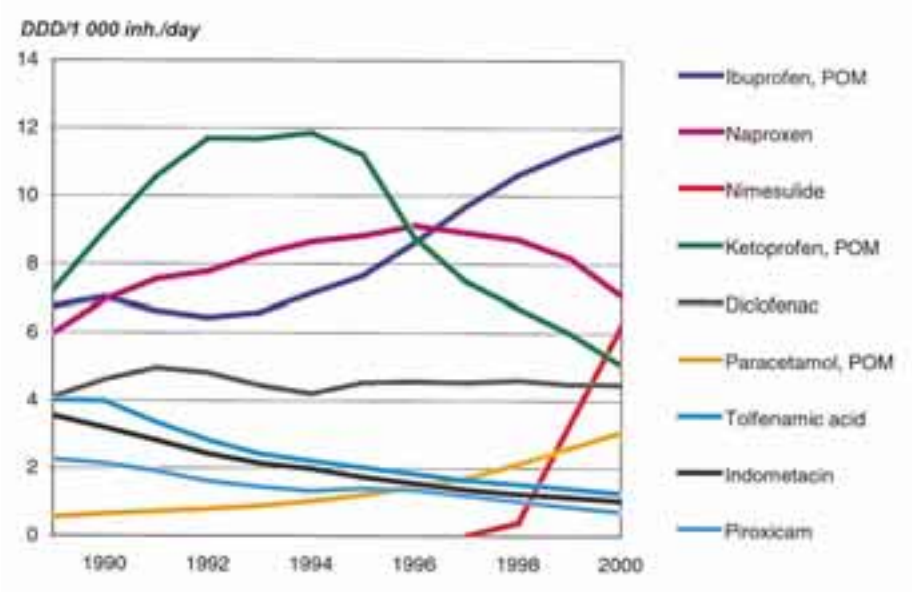
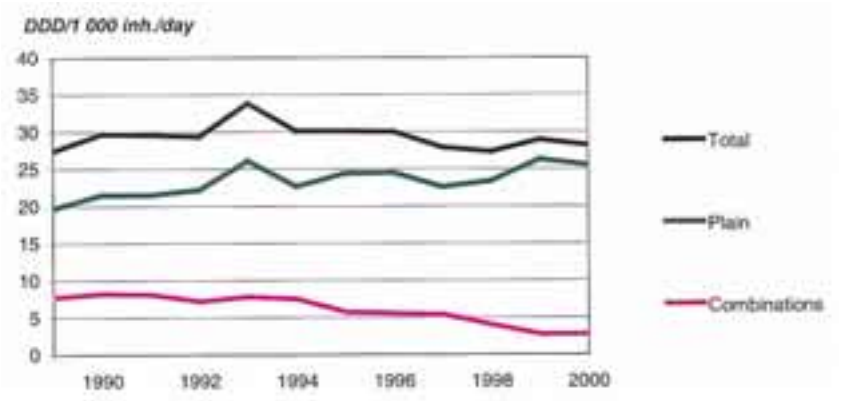


Fig. 3. ***Consumption of OTC preparations*** *(DDD/1,000 inhabitants/day).*



been the most commonly used anti-inflammatory OTC drug (Fig. 4-5).

Ketoprofen became an OTC drug in 1992. At first, its consumption increased greatly until 1993; it then dropped in 1994, and a downward trend began again in 1996 (Fig. 4 and 5).

What influences the choice of drug?

A report based on an analysis of an extensive literature survey states that no significant differences can be found in efficacy between the various anti-inflammatory analgesics. On the other hand, the profiles of the adverse effects of the preparations differ more clearly from one another (3). The use of anti-inflammatory analgesics is associated with increased risk of GI bleeding. In has been estimated that the incidence of GI bleeding could decrease even by 70% if the NSAIDs with lowest risk would be used (4).

It could be assumed that the significance of adverse effects would be the key issue in the choice of drug. When the bases for choice of drug have been reviewed by classifying anti-inflammatory analgesics into low risk and high risk preparations in view of their gastrointestinal adverse effects, it has been found that the choice of drug in Denmark, Italy and Sweden varied between the countries to such an extent that the information compiled on adverse effects did not appear to control the choice (5).In Finland, the present consumption appears to favour anti-inflammatory analgesics with lower risk of GI bleeding.

The effect of the switch to OTC category

According to a report drawn up in Sweden, switches to self-medication made in 1980–1994 increased the consumption of these drugs by an average of 36% within two years of the switch. There were nevertheless large individual variations among the drugs. Consumption of the same drugs by prescription decreased by 26% at the same time (6). The report dealt with all the preparations which were switched to being available for self-medication, and was not targeted, for example, at analgesics.

A study in the USA discussed the effect of switching H_2 blockers to the OTC category according to the number of prescriptions issued. The study found that the reduction in the number of prescriptions of H_2 blockers was statistically significant. Nevertheless, the number of doctor's appointments arising from gastrointestinal diseases did not increase (7). Indirectly, it could be assumed that patients switched over to self-medication as and when it became possible. The sales of H_2 blockers by pre-

Fig. 4. ***Consumption of the most common anti-inflammatory OTC preparations*** *(DDD/1,000 inhabitants/day).*

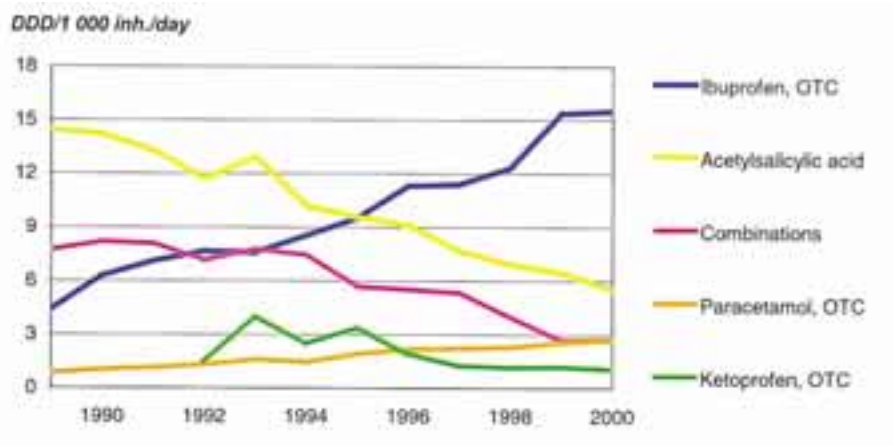
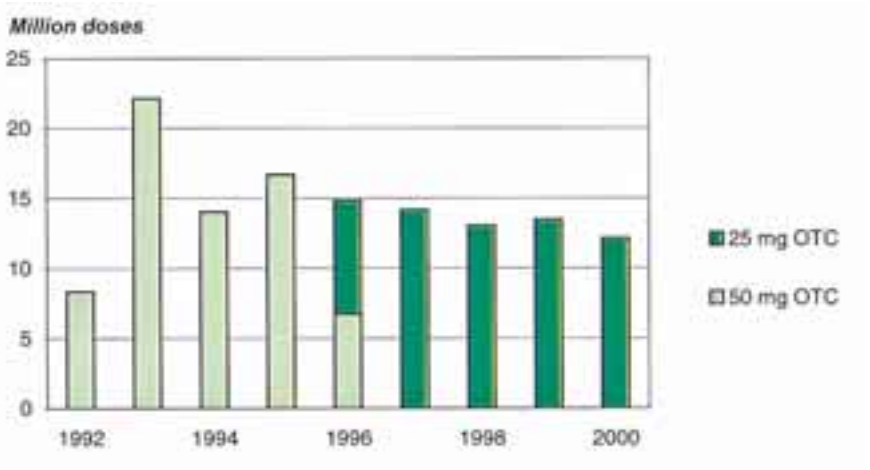


Fig. 5. ***Consumption of ibuprofen and ketoprofen*** *(DDD/1,000 inhabitants/day) during 1984–2000.*

Fig. 6. ***Consumption of ketoprofen in individual doses during 1992–2000.***



scription were also reduced in Finland when some containers were switched to the OTC range of drugs (8).

The consumption of prescription packages of ibuprofen dropped at the beginning of the 1990s, but started an upward trend again in 1993. This drop in consumption was linked in time with the switch of ibuprofen to self-medication. It is possible that the abolition of prescription status robbed the preparation of some of its placebo effect and doctors started prescribing other prescription preparations. This may partly explain the increase in prescribed consumption of ketoprofen detected at the same time.

The apparent increase in consumption of ketoprofen in 1993 is explained by the fact that in 1992 ketoprofen was sold as an OTC drug for only part of the year. The drop in 1994 can possibly be explained by the forceful marketing of the new OTC drug to pharmacies and consequent filling up of stocks during 1993. The stocks were still being sold to customers during 1994 and were not replenished at the same rate as that at which the drug was changing hands and being received by consumers.

The rapid increase in the consumption of prescription packages of ketoprofen moderated and it remained steady during 1992–1994. This recession in consumption occurs at the same time as the switch of small packages of ketoprofen to the OTC range. This recession in prescription drug consumption appears to have been similar to that reported during the switch of ibuprofen to the OTC range of drugs.

Ketoprofen 50 mg preparations were considered to be inappropriate for OTC sales and they were consequently returned to prescription only status in July 1996. These circumstances, and the discussion preceding them, may have been the cause of reduced popularity of ketoprofen.

A survey based on the values of DDD/1,000 inhabitants/day gives a somewhat misleading picture of the switch back to prescription status of the 50 mg packages. The consumption (DDD/1,000 inhabitants/day) dropped by 68% between 1995 and 2000. Part of the drop is explained by the reduction in consumption, but part of it can be explained by the shift to a lower strength. Looking at the number of sold doses (tablets, capsules) in OTC use, the drop has only been 27% (Fig. 6). Subsequently, the number of drug doses used in self-medication did not drop as much as an examination of the DDD values (150 mg) suggests. The previously used strength of 50 mg in self-medication was replaced by 25 mg. The consumption and sales of ketoprofen OTC have remained fairly steady since 1996.

Conclusions

During the survey period, various circumstances and factors associated in particular with ketoprofen may explain its present position on the anti-inflammatory analgesic market. Based on the information from this survey alone, it is impossible to say which factors have been decisive at their respective points in time. After sharp rises and falls in sales figures in the first years, ketoprofen appears to have attained a steady sale in the OTC market.

The sales and consumption of ibuprofen have been characterised by a constant upward trend. Its sales as a prescription drug dropped slightly only at the beginning of the 1990s. This may have been associated with its switch to OTC use. The situation changed thereafter and ibuprofen is today the most commonly used anti-inflammatory analgesic, both OTC and by prescription. In OTC use, the consumption has switched from ASA and its combination preparations to ibuprofen.

In the light of the survey it can be established that

- the total consumption of anti-inflammatory analgesics has remained fairly steady during the entire survey period.
- switching from one drug to another does occur. While ibuprofen has gained large popularity, the use of other anti-inflammatory drugs has decreased.
- the consumption is not automatically increased by a switch to OTC use, but consumption is influenced by several factors. This can be seen by examining the curve of development of sales of ketoprofen.
- a switch to OTC use appears at least temporarily to diminish the consumption of the drug by prescription.

Literature

1. Voipio T (2001) Itsehoitoon siirretyt tulehduskipulääkkeet – vaikutukset käyttömääriin ja kustannuksiin. Loppuтyö Helsingin yliopisto, sosiaalifarmasia

2. Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carlson JL, Griffin M ym. (1996) Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 7046:1563-1566

3. Gøtzsche P (2000) Extracts from "Clinical Evidence": Non-Steroidal anti-inflammatory drugs. BMJ 7241:1058-1061

4. Langman MJ (2001) Ulcer complications associated with anti-inflammatory drug use. What is the extent of the disease burden? Pharmacoepidemiol Drug Saf 10 (1):13-19

5. Bergman U, Andersen M, Vaccheri A, Bjerrum L, Wettermark B, Montaro N (2000) Deviations from evidence-based prescribing of non-steroidal inflammatory drugs in three European regions. Eur J Clin Pharmacol 56(3):269-272

6. Carlsten A, Wennberg M, Bergendal L (1996) The influence of Rx-to-OTC changes on drug sales. Experiences from Sweden 1980–1994. J Clin Pharm Ther 22(2):155-156

7. Andrade SE, Gurwitz JH, Fish LS (1999) The effect of an Rx-to-OTC switch on medication prescribing patterns and utilization of physician services: the case of H_2-receptor antagonists. Med Care 37(4):424-430

8. Martikainen J, Voipio T (2000) Mahahaava ja närästyslääkkeiden käyttö 1990-luvulla, TABU–Lääkeinformaatiota Lääkelaitokselta 6:17-18

Translation Mervi Moisander