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Editorial

Generic substitution is expanding

The reforms in 2002 of the Medicines Act and the Sickness Insurance Act imposed on the National Agency for Medicines in Finland the responsibility for preparing a list of medicinal products which are substitutable for one another since they contain the same amount of the same active substance, and which are biologically equivalent. In October 2002 NAM formulated the principles for preparing a list of generically substitutable medicinal products, and published the first list on its website in February 2003. Generic substitution was subsequently introduced in Finland in April 2003.

The list was initially prepared with the consideration in mind that substitution could be carried out without compromising patient safety and without interfering with treatment compliance or undermining the confidence among the various parties. The preparation of this list proved successful. The principles of preparation have remained almost unchanged for the past three years. The first list contained 1,502 products with marketing authorisation, representing 217 active agents or compound groups and covering about 31% of all medicinal products. The corresponding figures in the list established for the first quarter of 2006 are 3,205 medicinal products, 270 medicinal substances, and 49% of all medicinal products.

According to our experience at NAM, the principles of preparation of the list have not been jeopardised, the lists have been submitted on time, and an additional service has been offered to the parties concerned, namely, free access to the database from which the lists can be downloaded. NAM has ensured that medicinal products of high quality only are introduced on to the Finnish market: the quality of generically equivalent products is evaluated using the same criteria as is applied to the original product, pharmaceutical manufacturing is regularly inspected by the authorities, and the biological equivalence of generic medicinal products is shown by clinical studies or comparable absorption studies.

The reform of the Medicines Act in November 2005, and the three-year experience of generic substitution so far, have been used as the basis for updating the principles of preparation of the list and expanding the criteria for substitution.

From the beginning of 2006, the principles of generic substitution will include the conception that different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance, can under certain conditions, be considered as the same active subtance, and therefore be substitutable as long as the rest of the substitution criteria are fulfilled. In the marketing authorisation application procedure, pharmaceutical formulations with immediate release of the medicinal substance have for years been considered as equivalent products (tablets and capsules of various forms), and now the same principle is being applied to generic substitution.

The area of generically substitutable formulations has been expanded to include prolonged-release tablets and capsules, ointments and shampoos. Prolonged-release tablets and capsules may be interchangeably substitutable with one another, in the same way as gastro-resistant tablets and capsules are, as long as the rest of the conditions of equivalence are fulfilled. Antipsychotics and antidementia drugs are nowadays also considered generically substitutable. Parallel distribution referring to parallel imports in the centralised procedure has been added to the terminology.

Nowadays, doctors, patients, pharmacies and the pharmaceutical industry are all familiar with their rights and responsibilities in relation to generic substitution of drugs. A doctor may as necessary forbid the substitution on medical or therapeutic grounds. Consideration in the prescribing of generically substitutable drug products should still be focused on the patient's hypersensitivity, difficulties in controlling the level of the disease, compliance with the treatment, and any errors of medication that may occur. The patient always has the right, without giving a reason, to refuse a generic substitute; the refusal will have no effect on the amount of reimbursement that he or she is entitled to from the Social Insurance Institution in Finland.

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Common sense comes up trumps in the withdrawal of benzodiazepines

If a patient has been on benzodiazepines or short-acting hypnotics for several weeks, critical assessment of the need for medication should be a priority. Total withdrawal is not always the unconditional target, but initiation of the withdrawal process is recommended if the adverse effects of medication outweigh the benefits. If dependence has developed, sudden discontinuation of medication is advised against. The use should be tapered out gradually during several weeks, sometimes even months. It is always preferable that the prescription for benzodiazepines should be issued by one and the same doctor.

Benzodiazepine dependence is characterised by tolerance, i.e. gradually reduced efficacy, attempts to increase the dose, withdrawal symptoms as a result of dose reduction and continuation of use despite the adverse effects.

In practice, there are three common forms of benzodiazepine dependence (1). **Dependence at usual therapeutic doses** (small dose dependence) is iatrogenic. It occurs in the elderly or in patients on long-term therapy after years of use: about half of the patients in these groups are affected. **In escalating dependence** the use may have started as a common therapy, which is never discontinued, followed by gradually increased doses. These patients may in fact have appointments with several doctors. In Finland, 2–3% of patients on CNS drugs belong to the risk group of drug addiction. **In the mixed use of intoxicants**, attempts are made to increase the effects of other intoxicants or to alleviate the withdrawal symptoms with benzodiazepines.

Harmful use of benzodiazepines is not characterised by dependence, but by bodily or mental harm caused by the use, e.g. behavioural or memory disturbances. Distinctive findings can be detected among the withdrawal symptoms of benzodiazepines (see Table), and insidiously occasionally even delirium a couple of weeks later. The withdrawal symptoms of use include, in theory, symptoms of recurrence (relapse, i.e. the original anxiety syndrome recurs), and rebound symptoms (transient exacerbation of the original symptoms) as well as the actual withdrawal symptoms (2).

First examine the real nature of the use

The actual size of dose and duration of therapy are established at the start of the therapy. Data is collected from all previous situations of treatment. The patient's motivation for use and withdrawal are examined by interview. The benefits and adverse effects of the medication are openly discussed with the patient. Long-term use at least appears to benefit the patient if the treatment continues. Some-times no other treatment is adequate in the control of symptoms of anxiety or sleep disturbance, or the medication is clearly beneficial in the treatment of a concurrent psychiatric or neurological illness of the patient (1, 2, 3).

The harmful effects of long-term use usually clearly outweigh the benefits (1, 3, 4, 5). Dependence may develop with any benzodiazepine. They have a sedative effect and expose at least a proportion of patients to accidents. They cause disturbances of the cognitive function, confusion and agitation, especially in dementia patients. They occasionally reduce impulse control, thereby exposing the patient to association between the use of intoxicants and aggressiveness. Benzodiazepines may increase the urge to drink alcohol in intoxicant users; they also penetrate the placenta. Overall, they are harmful in traffic and working life, which the patient may not always be aware of. Generally only higher doses are life-threatening, while, on the other hand, even minor mixed use with alcohol can cause unexpected reactions. Their benefit as sleeping aids has been proven only in short-term use. There is no evidence that benzodiazepines would be beneficial in the treatment of alcohol dependency (6).

Withdrawal is associated with several benefits. First of all, it is not until after the withdrawal that a realistic picture of the need to use the drug is formed (2). Overall, the patient gets rid of unnecessary or harmful medication with subsequent improvement of life quality.

An open discussion with the patient about the diagnostic criteria, withdrawal symptoms (see Table) and benefits and adverse effects of the medication is beneficial. Existing psychiatric disorders are established and treatment introduced as necessary. In the presence of symptoms of mood swings or anxiety disorders, any anti-

depressant or other medication is recommended to be introduced at least 2–3 weeks before starting the withdrawal of benzodiazepines.

Withdrawal is not an unconditional end in itself, because it may also be harmful. Controlled long-term use may be possible if the adverse effects of withdrawal outweigh the benefits expected. Transient increase in anxiety and sleep disturbances may occur, especially if the withdrawal has been too quick. Withdrawal requires motivation, time, patience and collaboration, also on the part of the doctor (4, 6). Withdrawal is recommended if it is expected to improve the condition of the patient.

Treatment by one physician

At the health centre outpatient clinic patients are given an appointment with their own doctor. Prescriptions for sedatives are not issued as a rule in an outpatient situation, but acute medication for withdrawal symptoms is always prescribed if required (7). Any symptoms resulting from withdrawal of intoxicants or medicines are only treated if objectively found. Threatening behaviour is not a withdrawal symptom, and the patient may be asked to return to the appointment later, or institutional therapy may be recommended.

In primary health care, withdrawal may be started if the dosage is no higher than about one and a half times the official recommended maximum dosage, the patient is not suffering from a severe psychiatric illness, is not a user of a mixture of intoxicants and complies with the treatment plan. Request for a consultation with a psychiatrist is recommended if collaboration with the patient is poor, or there are signs of a severe personality disorder, or if there is a question of a severe depression, a severe anxiety disorder or a history of a psychotic illness. If medication with benzodiazepine is continued for more than four months without withdrawal, it is recommended that the opinion of a psychiatrist should be sought, to ensure that the diagnosis is correct and to check the availability of alternative therapies.

A consultation with a psychiatrist or a doctor specialising in intoxicants, or a referral to an 'A clinic' [an outpatient clinic for intoxicant users], is recommended if previous attempts at withdrawal have failed, or the initial daily dose is about one and a half times the official recommended maximum dose, or if benzodiazepine medication exceeding the recommended maximum doses is continued without attempts at withdrawal; weighing up the adverse effects and the benefits, for example, may be the reason for the consultation. An 'A clinic' is the appropriate place for treatment if the patient is a user of a mixture of intoxicants and a large-scale consumer of alcohol. Consultation with a neurologist is recommended if the patient has a neurological illness the treatment of which would benefit from benzodiazepines.

It is recommended that withdrawal, or at least the initiation of it, be carried out under institutional care, such as in a health centre in-patient ward, a social hospital or a psychiatric ward, if the initial dose of benzodiazepine is more than twice the official recommended maximum dose (severe high-dose dependency), the idea of the initial dose is uncertain, the patient is dependent on several intoxicants or uses a mixture of them (6), the patient has other severe illnesses such as severe sleep apnea, coronary artery disease, severe depression, or the patient is using barbiturates.

The treatment management plan is set out in writing

The management plan for long-term use or withdrawal is drawn up in writing. A copy of an entry in a patient record is adequate if the patient can sign it. It is important to obtain the patient's written permission to collect the data from previous places of treatment, to obtain permission to forward immediately to all previous places of treatment a copy of the management plan, followed later by information about its progress, or cancellation, together with permission to request an extract from the registers of the local pharmacies with details of the client's medicines purchases over the previous six months. During treatment the patient will undergo random testing consisting of blowing into an alcometer or screening for narcotics. The patient is advised in advance that any lost or stolen prescription will not be replaced; any objectively diagnosed acute withdrawal symptoms will be treated as necessary in the emergency room.

In complicated cases – if the dose differs from the official dose recommendations, or if the centralisation of treatment is suspected to be failing, or if the withdrawal attempts have repeatedly failed – an agreement called the pharmacy agreement will be made. The patient may be asked to keep a diary of the use of medicines. The patient will at the same time identify any risk situations caused by excessive use and consider other means of management (6).

Establishing the initial dose

At first, a daily dose is determined which will allow the patient a sufficient amount of sleep and does not cause withdrawal symptoms such as tachycardia, hypertension, tremor and sweating (see Table). Withdrawal symptoms may also be evaluated by a scale called CIWA-B.

In institutional care the dose is initially increased by as much as 20 mg of diazepam at 2-hourly intervals (up to 200 mg/24 hours), but only if withdrawal symptoms are perceptible in the patient's condition and the patient is not sedated at all. Very high initial doses can in most cases be reduced (in institutional care) by half within about a week, especially if the patient is using diazepam. The dose may be reduced evenly, or in relation to the severity of the withdrawal symptoms; there is no essential difference between these methods in institutional care. In severe high-dose dependency carbamazepine or valproate may be used as a supportive medication (5). If a previous attempt at withdrawal has failed, or the patient is prone to exhibit withdrawal symptoms, or the drugs used are very short-acting, then the therapy can be replaced, overlapping with diazepam in accordance with the equivalent doses over a period of 1–2 weeks.

Withdrawal of low- and high-dose treatment

If the initial dose exceeds the official recommended maximum dose, it is usually possible to reduce the daily dose by 10–25% at intervals of 1–2 weeks. The recommended maximum

Withdrawal symptoms associated with benzodiazepines

Affective syndrome and cognitive disorders
- *Anxiety, fearfulness*
- *Nausea, irritability*
- *Pessimism*
- *Recurring obsessive/compulsive thoughts, mistrustfulness*

Sleep disorders
- *Sleeplessness, disturbed day and night rhythm, daily fatigue*

Physical symptoms and findings
- *Tachycardia (pulse over 100/min.), hypertension*
- *Hyperreflexia, muscular tension, tic, tremor, ataxia*
- *Agitation, motor restlessness*
- *Myalgia, arthralgia*
- *Nausea*
- *Sweating*
- *Tinnitus*
- *Grand mal seizures*

Perception disorders
- *Experiences of depersonalisation (feelings of estrangement)*
- *Loss of visual acuity, improved sense of hearing*
- *Illusions, hallucinations*

dose is about 40 mg of diazepam, 120 mg of oxazepam or 6 mg of alprazolam per day. When the dose is approximately the recommended maximum, or below it, the reduction in dose is carried out carefully by 10–20% at intervals of 2–3 weeks (1). Sleeping aids should also be withdrawn gradually.

Should mild withdrawal symptoms occur, the dose should not be increased back to its previous level, but instead a longer delay should be observed until the next reduction (2, 4). Withdrawal symptoms develop within 1–2 days after the discontinuation of short-acting, and not until within 2–14 days after the discontinuation of long-acting, benzodiazepines. It is recommended that any sedatives otherwise usually taken as required be avoided at this stage, and regular medication should be aimed at. The patient is seen at appointments at monthly intervals, more frequently at the beginning, withdrawal symptoms are openly discussed and the patient is encouraged to continue the withdrawal (1, 2, 8).

The rate, unlike the target of withdrawal, may be relaxed as necessary. The patient will benefit from follow-up appointments even after completion of the withdrawal. Relapses are a risk, and the occurrence of other psychiatric symptoms may require appropriate treatment (1, 8). Severe personality disorders undermine the prognosis, at least in users of a mixture of intoxicants.

If withdrawal fails

Should the withdrawal fail, the doctor should not blame the patient, but instead, always encourage the patient to try again. The situation is reported to other places of treatment in accordance with the treatment management plan. Supportive medicines are usually of only little benefit, but they may be tried, especially if a previous attempt at withdrawal has failed (1). For example, propranolol 10–20 mg (40 mg if necessary) administered 2–3 times a day, is beneficial in the treatment of somatic excitation symptoms of the autonomic nervous system. Valproate, carbamazepine and possibly also gabapentin may somewhat alleviate withdrawal symptoms or at least improve the outcome of treatment and inhibit seizures. Sedative antidepressants (mirtazapine, mianserin, amitriptyline) alleviate sleep disturbances (5), similarly to the administration of 25–100 mg of hydroxyzine (3). Imipramine supports the withdrawal in patients with generalised anxiety disorder. The efficacy of buspirone is inadequate in most cases in patients dependent on medicines (4), but positive experiences have also occurred in patients with generalised anxiety disorder. Melatonin (a dose of 2–6 mg administered at night) has occasionally been beneficial for sleep disturbances at the withdrawal stage. The use of dexmedetomidine under the supervision of an anaesthetist has alleviated the severe withdrawal symptoms of benzodiazepines and opioids, even in the case of a child. It should always be borne in mind that supportive medicines also have their adverse effects and contraindications.

Drug dependency is preventable

When introducing benzodiazepines or other sleep aids, it is recommended that the point in time at which the medication will be stopped should be agreed mutually with the patient (4). Other alternative therapies should always be sought for the treatment of anxiety or sleep disturbances. Naturally, attempts should be made to use the smallest possible dose. If the drug dose is small, even a simple recommendation by the doctor to reduce the medication may work as an encouragement for the patient to reduce the medication or to have breaks in the course of treatment.

Benzodiazepine derivatives cause dependence in various ways. Consequently, in all except acute therapies, oxazepam or chlorodiazepam would be preferable (since the effect will not start too quickly), and the drugs to be avoided include, for example, diazepam, lorazepam and alprazolam (4, 5), at least in patients with dependency. High-dose prescriptions should be avoided with preference given to renewals. If the prescription is lost, a renewal cannot be issued.

The grounds for long-term use started earlier should be assessed and determined at least annually (4, 6). The attitude should not be moralising, but critical. All except emergency units could adopt the principle of never prescribing benzodiazepines at first appointments; this information can also be made readily available to the patient.

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ASCOT – the most extensive hypertension trial

The results of ASCOT (the Anglo-Scandinavian Cardiac Outcomes Trial) have received wide public circulation. Some communications have focused on the significant reduction in cardiac mortality, while the most important change in fact involved the reduction in the number of strokes.

Hypertension trials have generally compared a new drug therapy with a diuretic, to be used as a medication called 'current antihypertensive medication'. The drug of comparison has often been atenolol 50 mg once or twice daily and bendroflume-thiazide 2.5–5.0 mg per day, corresponding to 25–50 mg of hydrochlorothiazide.

The hypothesis of ASCOT was that by using a vasodilator therapy, consisting of amlodipine as necessary as a combination treatment together with an ACE inhibitor, perindopril, the number of non-fatal and fatal cardiac infarctions would be reduced. The trial was planned in 1990 and started in February 1998. The statistical power of the trial was judged by suggesting that this type of cardiac event would occur in 2% of the patients in the beta-blocker group and that the vasodilator therapy would reduce the number of cardiac infarctions by 15% in comparison with the atenolol-thiazide group. The estimated power of the trial was 80% with 5% confidence limits. It was generally recommended at the planning stage of the trial that the hypothesis and statistical power of the trial should be designed so that the hypothetical model would be superior to the control group. Consequently, the non-inferiority principle, i.e. equivalence of the end points, was not used in the planning of the statistical analysis of ASCOT.

In addition to hypertension, at least three of the following factors which increase the risk should be present in the patients entered in the trial: smoking, left ventricular hypertrophy, male sex, coronary artery disease in the relatives, diabetes, microalbuminuria, over 55 years of age, history of a cerebrovascular accident, some other vascular disease, or lipid metabolism disorders. Excluded from the trial were patients with a history of cardiac infarction or who were on medication for symptomatic coronary artery disease. Patients who had suffered a stroke during the previous 3 months were also excluded from the trial.

During the trial, amlodipine was used for 82% and perindopril for about 50% of the duration of the treatment course. At one year into the trial atenolol was being used by 87% of the patients and by 79% of the total duration of the trial. Diuretics were administered to 66% of the patients. The third drug administered to some patients in both groups was alpha-blocker doxazosine, and in the diuretic group it was doxazosine and/or spironolactone.

The trial comprised patients who had other risk factors, except for symptomatic or otherwise diagnosed coronary artery disease. The drug of comparison consisted of a high-dose thiazide and a beta-blocker. The dose of atenolol used was that for patients with symptomatic bradycardia, which was suffered by 6% of the patients.

The estimated duration of the trial was around 3.5 years, but since the frequency of cardiac infarctions was reduced during the trial it was prolonged to almost six years.

ASCOT was not interrupted because of a risk of cardiac infarction, but on the recommendation of the safety committee, because, in the first instance, the number of strokes was higher in the beta-blocker group, and finally, because even the total mortality rate was smaller in the amlodipine group. The number of cardiac infarctions was not, however, decreased markedly.

There were 429 primary end points in the amlodipine group, and 474 in the atenolol group; while the non-standardised reduction in risk was 10% ($p< 0.1$). The number of events involving stroke was 23% lower in the amlodipine group (327/422). The reduction in numbers of all cardiovascular events and procedures was 16% with amlodipine therapy. The total mortality rate was 738 in the amlodipine-perindopril group and 820 in the atenolol-diuretic group, the reduction in risk being 11% ($p=0.025$). New cases of diabetes emerged clearly more frequently in the atenolol group, i.e. 799, whereas in the amlodipine group it was 567; the reduction in risk in the vasodilator therapy was –30%, $p < 0.0001$. This is a very important and noteworthy result, because diabetes is an important risk factor in cardiovascular diseases. During the first two years there were no differences in the numbers of cardiac infarctions, and only a small difference emerged in respect of the vasodilator therapy at a later follow-up stage.

In relation to treatment practices in Finland, the result of ASCOT clearly supports the notion that the primary

medication in patients who do not suffer from coronary artery disease, cardiac arrhythmia or hyperkinesia, which require beta-blocker therapy, could be vasodilator therapy.

The average age of patients in the trial was 63 ± 8 years. The conclusions are therefore not directly applicable to elderly persons, the recommended treatment in whom remains a low-dose diuretic. Neither should the result of the trial be interpreted in a way that would exclude the use of a beta-blocker as an antihypertensive agent. In response to tachycardia or bradycardia a beta-blocker therapy may be useful, and it is very appropriate in combination therapies.

Previous beta-blocker trials have been based on high-dose beta-blockers. In practice, they are nevertheless prescribed according to pulse rate response in smaller doses than in extensive treatment trials, and most patients are also on a vasodilator agent.

It should be noted that a large proportion of patients with hypertension suffer from cardiac arrhythmia, atrial fibrillation, tachycardia or palpitations, and coronary artery complications. As a rule, the practical arrangements for individual therapy for hypertension in Finland are good.

It is clear, however, that beta-blocker and diuretic therapies, especially with high doses of atenolol and thiazide, are associated with an increased risk of diabetes. This confirms the main practice prevalent in Finland for years, i.e. that the daily dose of hydrochlorothiazide should be 12.5–25 mg.

The statistics of the National Agency for Medicines in Finland show that the use of ACE inhibitors and angiotensin receptor blockers as well as of calcium channel blockers and beta-blockers has increased in recent years. In patients recently diagnosed as having hypertension and patients with no tachycardia or hyperkinesia, and also in long-term complications of hypertension, the preferred treatment has consisted of a vasodilator therapy alone or combined with a low-dose thiazide, including a beta-blocker later on as necessary. Consequently, the results of ASCOT cannot be interpreted as having had a significant effect on the number of serious events in Finland, but instead, the results are supportive of the present practice of individual therapies.

Is there a difference between the ACE inhibitors and/or amlodipine?

It is clear that an ACE inhibitor is the choice more to be recommended in patients with occasional oedema, especially if the patient suffers from cardiac insufficiency. There is no need to change the calcium channel blocker of the amlodipine type if the response has been good and especially if no other medication is necessary. High doses of thiazide and/or beta-blockers should be avoided, because several studies show that they increase the risk of diabetes and stroke. This leads to less exercise and a weight increase usually follows.

An evaluation of ASCOT should take into consideration the patient material selected and the hypothesis. In addition, it is important to compare this with our practice and amend our recommendations, which are already making a specific attempt to avoid high-dose thiazide therapies. A beta-blocker is probably used as a rule because of its other effects in hypertensive patients, and the dosage is adjusted individually.

In the treatment of hypertensive patients it should be borne in mind that a good control of any additional risk factors, especially a control of the cholesterol level with diet and medication, achieves the biggest reduction in heart attacks.

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Tamsulosin-induced iris complications associated with cataract operations

Tamsulosin is a selective antagonist of α_{1A}-adrenoceptors, the main indication for which is treatment of symptoms of benign prostatic hyperplasia. The use of tamsulosin in Finland is fairly extensive (6.6 DDD/1,000 inhabitants/day in 2004 with the defined daily dose of 0.4 mg). Sufferers from symptoms of prostatic hyperplasia are often of the same age group as those who need a cataract operation.

A recent paper in the Journal of Cataract and Refractive Surgery has described a syndrome associated with the use of tamsulosin and occurring during cataract surgery; the authors have named it the IFIS (Intraoperative Floppy Iris Syndrome) (1). It is a question of retrospective data in which 3% of the cataract patients have been on tamsulosin therapy. A retrospective survey has shown that the syndrome could be found in 10 out of 16 users of tamsulosin, but in none of those who had used other systemic α_1-antagonists. One patient with diagnosed IFIS had not, so far as is known, used tamsulosin or any other α_1-antagonist. One patient with IFIS had discontinued the use of tamsulosin one year, and another patient three years, prior to the cataract operation. The authors presumed that the iris hypotension, which had continued for so long after discontinuing the medication, would be a result of diffuse atrophy of the dilator pupillae muscle of the iris, caused by tamsulosin therapy.

Konno and Takayanagi (2) and Nakamura et al. (2) found that, in rabbits, the contraction of the dilator pupillae muscle of the iris is transmitted via the α_1-adrenoceptors. The subtype of α_{1A}-adrenoceptors is found to dominate in the iris, chorioid and retina (4). *In vitro* studies showed 12–20-fold tamsulosin affinity with α_{1A}-adrenoceptors compared with α_{1B}-receptors, and 2–3-fold compared with α_{1D}-receptors (5, 6, 7). In a study on dogs by Sato et al. tamsulosin concentration in plasma was found to decrease following oral administration and to reach the lowest measurable limit within 4 hours, whereas the concentrations in the prostate and the urethra remained at the level of 13–44-fold (8). This is considered to have resulted from the long-term binding of tamsulosin to the target tissues.

During the past few years, male cataract patients have increasingly been identified as having an iris with abnormal behaviour during surgery; a floppy iris which has made surgery more complicated. Once it emerged that a common factor in these patients was tamsulosin therapy, a study with the aim of explaining the mechanism of this adverse effect was initiated in spring 2004 at the Central Hospital of Keski-Suomi in collaboration with the University of Kuopio, Department of Pharmacology. Preliminary results of the study have recently been published in the journal Acta Ophthalmol Scand (9).

By the time of publication of the study all seven operated patients (and by today, all of the 17 patients in total), who had been using tamsulosin, had been found during surgery to have IFIS, i.e. a floppy and sail-shaped iris, while normally the pupil during a cataract operation is highly dilated and the iris is very elastic, so that it stays well in place during surgery and does not prolapse through the operation apertures. Six out of seven patients on tamsulosin therapy were found to have suffered a prolapsed iris during surgery, and in four patients the iris tended to get tangled in the tip of the phaco equipment used during surgery (9). Furthermore, the pupil was poorly dilated and became further significantly contracted in six patients out of seven in the course of the surgery, thus complicating the performing of the operation.

The phenomena described above complicate cataract operations significantly and increase considerably the risk of other complications associated with surgery. An iris prolapsed through the operation apertures may rupture or become damaged and therefore result in a deformed pupillary aperture, or the pupil will no longer contract and dilate normally. In their patient data, Chang and Campbell (1) also described cases where the posterior capsule of the lens was ruptured, and loss of vitreous body occurred in 12% of their operations. My own patient data do not include complications associated with the posterior capsule.

In a cataract operation the pupil is dilated by depressing the pupil contracting sphincter pupillae muscle by the use of parasympatholytic drops (having as the active agent either cyclopentolate or tropicamide). The dilation of the pupil is facilitated by stimulating the sympathomimetically innervated iris dilator muscle by using drops of sympathomimetic metaoxedrin. It appears that tamsulosin is strongly bound in the post-synaptic receptors of the iris dilator muscle and

thereby inhibits the dilatation of the pupil. Long-term use of tamsulosin could result in dilator muscle atrophy, which would explain the IFIS.

Chang and Campbell (1) recommended that patients on tamsulosin therapy have a break in their medication for 1–2 weeks prior to their cataract operation. I have myself recommended a few patients to have breaks of variable durations, from 1 to 4 weeks, but even a 4-week break in medication has not so far removed the phenomenon; while severe urinary retention occurred in one patient even after a one-week break in medication.

When prescribing tamsulosin, doctors are advised to bear in mind that the drug causes complications in any forthcoming cataract operations. In addition to other drugs, it is also suggested that surgeons pay attention to the complicating effects of this drug in particular in surgery. In future, further explorations are recommended into how, by modifying the cataract operation, the above complications caused by tamsulosin could be further reduced.

The adverse drug reaction register of the National Agency for Medicines in Finland has received three reports of tamsulosin-induced iris complications which occurred during cataract surgery. All of the patients were males over 70 years of age and on tamsulosin therapy for benign prostatic hyperplasia. In all of the patients, the cataract operation had become technically highly difficult, but permanent damage with adverse effects on the function of the eye did not develop in any of them. The adverse effect will be included in the updates of the SPCs and PILs of the preparations containing tamsulosin.

Thus far it is not known whether this is a class effect.

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