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Summary

Summary

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Collaboration boosts quality control in Europe

Specifications for pharmaceutical products are laid down and approved as part of the marketing authorisation procedures. Within the European Union, the marketing authorisations for medicines have since 1995 been granted through the centralised procedure, the mutual recognition procedure or through national authorisation. Although many innovative products go through the centralised procedure, the mutual recognition of national authorisations is more frequent a way to obtain marketing authorisation. In Finland, about one of every four medicinal products were centrally authorised last year. When medicinal products enter the market, the authorities perform laboratory tests to control that they really comply with the specifications imposed on them.

Since 1999, there has been an operation procedure, co-ordinated by EDQM (European Department for the Quality of Medicines), for sampling and testing of EU centrally authorised products. This is done in accordance with a program adopted by EMEA (European Agency for the Evaluation of Medicinal Products). Each product is examined by two laboratories, which are members of the European Network of Official Medicines Control Laboratories. That way the whole range of expertise of all member state laboratories can be fully utilised, while overlapping work and sampling can be avoided. The above, however, applies only to medicinal products that have undergone the centralised marketing authorisation procedure.

Due to the positive experiences from the inter-laboratory collaboration, it is now planned to extend it to the medicinal products authorised through the mutual recognition procedure. In December 2000, it was agreed at a meeting held in Strasbourg to initiate a trial project. This trial phase is now nearing its end, and an evaluation meeting is due to be convened early in the year 2002. The Pharmaceutical Laboratory of the National Agency for Medicines has actively participated in the planning and testing of new procedures. The work-sharing now under elaboration will boost quality control, as a laboratory can analyse samples coming from various parts of Europe in batches, instead of several national laboratories analysing each medicinal preparation separately. The procedure also enables comparisons between the results of the samples tested.

At present, a considerable part of the working hours of medicines control laboratories is spent on acquiring materials, supplies, and instructions and further on method validation and documentation. Taking several samples from different countries and analysing them simultaneously increases control efficiency, because the time spent on analysing a single sample, or a set of three or four samples, does not differ significantly.

This collaboration presupposes, however, that the mutual approval of results does not give rise to any problems for the participating authorities. Developing quality systems for the laboratories and accreditation of methods serve to increase the reliability and credibility of test results. Verifying the quality control test results in another laboratory would be desirable, at least until all participating laboratories have received accreditation. The Pharmaceutical and Biological Laboratories of the National Agency for Medicines are well equipped to participate in European quality control collaboration, regardless of in what direction the system develops. The laboratories have a quality system based on the standard EN ISO/IEC 17025, and their most important methods have been accredited by the Finnish Accreditation service, FINAS.

Summary

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Asthma not adequately controlled by inhaled steroids

It is characteristic of patients with moderate persistent "step 3" asthma (1,2) to have symptoms of asthma even daily, despite the use of low to moderate doses of inhaled steroids (beclomethasone or budesonide < 1,000 microg/day or fluticasone < 500 microg/day). Several doses of rescue medication are required weekly or even daily. Low and/or variable peak expiratory flow (PEF) values or low forced expiratory volume in one second (FEV_1) are often revealed by pulmonary function tests. The asthma is not adequately controlled and the treatment should be made more effective. The alternatives consist of increasing the dose of inhaled steroids or adding a long-acting beta-2-agonist, a leukotriene antagonist or theophylline to the treatment.

Find out

Before changing the medication find out

- whether the patient is using inhaled steroids in accordance with the instructions given
- whether the inhalation technique is correct
- if there are any deteriorating factors in the patient's environment (e.g. pets, changes in the working environment, hobbies)

If the points above give no cause for concern, or the circumstances cannot be changed despite attempts to do so, then the medication should be altered to make it more effective.

Should the dose of inhaled steroids be increased?

Increasing the dose of steroids could evoke several different anti-inflammatory effects which smaller doses are unable to produce, so in principle increasing the dose appears a sensible approach.

A statistically significant dose-response relationship has been reported in some studies (e.g. 3,4), but, surprisingly, an important difference only occurred between the smallest and the largest dose of budesonide (200–1,600 microg/day) when morning PEF values or FEV_1 (4) were measured. No important differences between the doses were found when evening PEF values, day- or nighttime symptom scores or the use of rescue medication were measured. Similar results have been obtained with beclomethasone and fluticasone in spite of even an 8 to 20-fold difference between the lowest and the highest doses of the drug (5,6). But, in respect of all the variables studied, the effect of the smallest dose of fluticasone (50 microg/day), for instance, was already markedly different from that of the placebo (5). A meta-analysis (N=2,324) (7) of the dose-response relationship of fluticasone in the treatment of asthma concluded that 80% of the benefits of a large dose of fluticasone (1,000 microg/day) were already obtained at a dose level of 70–170 microg/day and 90% of the benefits at a dose level of 100–250 microg/day. The maximum effect of fluticasone was obtained with a dose level of about 500 microg/day. In another meta-analysis (8) fluticasone was found to improve the results of pulmonary function tests and reduce the symptom scores and the need for the rescue beta-2-agonist use at all dose levels studied (100–1,000 microg/day) as compared with the placebo. Even in this case, the only important difference was between the doses of 100 and 1,000 microg/day. A meta-analysis (9) made of the studies on beclomethasone arrives at results pointing to the same direction. Budesonide (10) in mild or moderate asthma did not result in any significant dose-response relationship between dose levels of 200–1,600 microg/day when FEV_1, morning PEF values, symptom scores or the use rescue medication were measured. However, increasing the dose of budesonide from 200 microg/day to 800 microg/day in patients with moderate to severe asthma does lower the number of exacerbations of asthma. It seems therefore that the small and moderate doses of inhaled steroids used clinically nowadays are found in the flat part of the dose-response curve.

In the treatment of asthma, pulmonary function tests or asthma symptoms do not always give a reliable picture of the concomitant inflammation of the bronchi. Based on the limited studies published so far, it appears that the additional anti-inflammatory effect achieved by doubling the dose of inhaled steroids is generally not even statistically significant when inflammation is assessed by means such as hyperreactivity,

eosinophils, or exhaled nitric oxide (9,11-13).

The adverse effects of inhaled glucocorticoids are generally relatively mild. However, the risk of systemic adverse effects increases as the dose of inhaled steroids is increased. Adrenal suppression only seldom necessitates supplementation therapy, but it does reflect the possibility that inhaled glucocorticoids can cause other systemic adverse effects (14). The risks of reduced cortisol production and reduced bone density are markedly increased when the daily doses of beclomethasone dipropionate and budesonide exceed 1,500 microg and that of fluticasone propionate exceeds 750 microg (15). Nevertheless, the risk of systemic adverse effects varies individually. Even though the risk of adverse effects and their significance in long-term treatment remain largely unknown so far, attempts to use the smallest effective dose possible are certainly sensible.

Should a long-acting beta-2-agonist be combined to the treatment?

The bronchodilatory effect of long-acting beta-2-agonists, formoterol and salmeterol, lasts approximately 12 hours. Combining one of these with the steroid medication of asthma patients has been found to improve the patient's quality of life and the results of pulmonary function tests, decrease the night-time symtoms and protect from bronchial contraction caused by exercise or several unspecified factors more effectively than does a placebo or a regular use of short-acting beta-2-agonists (16). In recent years, several studies have been published in which the addition of a long-acting beta-2-agonist has been compared with increasing the dose of inhaled steroids in asthma patients in whom symptoms and/or findings typical of active asthma are found despite the administration of low or moderate doses of inhaled steroids.

Salmeterol

Adding salmeterol to the medication as against increasing the dose of inhaled steroids (doubling the dose, at least) have been compared in a recent meta-analysis (17). Adding salmeterol to the medication improves both the PEF values and the FEV_1 significantly better than does increasing the dose of inhaled steroids after both 3 months and 6 months of treatment. The addition of salmeterol to the treatment improved the PEF values by 22–27.7 L/min more and the FEV_1 0.08–0.1 L more than the increase in the dose of inhaled steroids did. The added salmeterol also increased significantly the number of symptom-free days and nights and the number of days and nights free of rescue medication use.

Formoterol

A one-year-long randomised double-blind study, FACET, examined the effect of two different doses of inhaled steroids (budesonide 200 and 800 microg/day) and of the addition of a long-acting beta-2-agonist (formoterol 12 microg x 2 /day) to the treatment in patients with symptomatic asthma despite the use of inhaled steroids (18). A statistically significant improvement of both FEV_1 and morning PEF values was obtained by a four-fold increase in the dose of inhalation steroids. Adding formoterol to the treatment improved both the FEV_1 and morning PEF values. The improvement produced by this combination is significantly larger than that following the increase in the dose of inhaled steroids. Adding formoterol to the medication also significantly decreased the daytime and nighttime symptoms and the need for symptom-relieving medication. An increase in dose of inhalation steroids also had a similar, although smaller effect. The adverse effects did not differ significantly to the advantage of either medication.

Exacerbations of asthma

Eosinophilic bronchitis is a typical feature of asthma. The biggest concern in the introduction of long-acting beta-2-agonists has been that they might mask an increase in the underlying inflammation in asthma. When the dose of the anti-inflammatory drug is not increased the underlying inflammation associated with asthma may be augmented and might finally result in increased number or more severe exacerbations of the asthma. The effect of addition of a long-acting beta-2-agonist on asthmatic inflammation has been examined in four studies (19-22). Three of these did not reveal any significant masking of the inflammation.

If the addition of a long-acting beta-2-agonist to the medication would mask the inflammation underlying the asthma, it could be expected to increase the number of exacerbations of asthma and/or make them more severe. Compared with an increase in the dose of inhaled steroids, the addition of salmeterol to the medication produced 2.7% fewer cases of exacerbation of asthma during 3–6 months of treatment (17), i.e. the addition of salmeterol did not increase the patient's risk of exacerbations of asthma. In the FACET study (18), a four-fold increase in the dose of budesonide decreased the number of exacerbations of asthma more than the addition of formoterol. The best result was obtained by increasing the dose of steroids simultaneously with the addition of formoterol: the number of exacerbations of asthma was decreased by about 60%. When the exacerbations reported in the FACET study were analysed separately (23), it was found that the addition of formoterol to the medication did not alter the changes in PEF values or symptom scores found during exacerbation. The important result of this finding is that PEF values can still be used in a guided self-management of asthma even in patients using long-acting beta-2-agonists. Guided self-management of asthma in itself decreases the number of exacerbations of asthma considerably (24). Taken together, there is no reliable proof that long-acting beta-2-agonists would have a significant additional anti-inflammatory activity in the treatment of asthma, but nor is there proof of the risk of significant masking of the inflammation underlying the asthma, if the patient is and remains on inhaled steroid therapy.

Should a leukotriene agonist be added to the medication?

A new group of drugs has been introduced into the treatment of asthma, cysteinyl leukotriene (CysLT1) receptor antagonists (montelukast and zafirlukast). The position of these drugs in the treatment of asthma has not yet been fully established (1,2). Leukotriene antagonists decrease bronchial constriction and improve pulmonary function. They also have a slight anti-inflammatory effect. Glucocorticoids have been reported to diminish the production of cysteinyl leukotrienes only slightly or not at all. By the addition of a leukotriene antagonist to the medication of asthma patients we would produce a preventive effect in the transmitter system on which the inhaled steroid has a only slight effect or no effect at all (25). But is it successful? In patients who had moderate symptomatic asthma despite being on inhaled steroid therapy, the addition of montelukast (10 mg/day) to the medication was compared with a placebo (26). The addition of montelukast improved the FEV_1 by 0.14 L and morning PEF values by 10.4 L/min, and there was a statistically significant decrease in the number of days of exacerbation and in the daytime asthma symptom scores. But, on the other hand, there was no statistically significant difference in the use of rescue medication, evening PEF values, the number of asthma attacks and the patient's own assessments. In patients who had symptomatic chronic asthma (27) despite inhaled steroid therapy and other medication (some patients were on a long-acting beta-2-agonists and/or theophylline), montelukast (10 mg/day) was no better than the placebo in reducing the patients' symptoms or the use of rescue medication or in improving the morning or evening PEF values. No significant benefit was proven by the addition of montelukast to the medication in this patient group, which bore a fairly good resemblance to patients at a normal asthma clinic run by a specialist.

The effect of the addition of high-dose zafirlukast (80 mg x 2) was studied in patients who had moderate or severe symptomatic asthma despite inhaled steroid therapy (28). The addition of zafirlukast to the medication improved the morning PEF values and FEV_1; the reduction in the symptom scores and in the use of rescue medication was also superior to that achieved by the placebo. Nevertheless, there was no significant difference in the nocturnal wakenings and the symptoms of asthma in the morning. The addition of zafirlukast reduced the risk of exacerbation of asthma (all stages of severity) significantly, the risk relationship being 0.61 in favour of addition of zafirlukast. According to a recent meta-analysis (29), compared with inhaled steroids alone, the addition of a high-dose leukotriene antagonist (2–4 x the normal dose in clinical use) to the medication reduces the occurrence of asthma exacerbations, which require a course of treatment with steroid tablets (the risk relationship being 0.34). The effect that normal therapeutic doses of leukotriene antagonists nowadays in use in Finland have on the number of exacerbations has not been studied. In adult asthma patients with symptoms, the addition of zafirlukast was no better than doubling of the dose of inhaled steroids in reducing the number of exacerbations (29).

The addition of montelukast (10 mg x 1) has also been compared with the addition of salmeterol (30, 31). Most measured parameters were considerably improved by both of these treatments. The addition of salmeterol appeared to improve the asthma control statistically significantly better than the addition of montelukast did, in respect of most parameters studied. However, not all symptom score parameters revealed a difference between the treatment groups. Similar results were obtained when comparing the addition of salmeterol to zafirlukast (20 mg x 2) in patients with moderate asthma (32).

To conclude, addition of a leukotriene antagonist to the medication of patients who exhibit symptoms in spite of inhaled steroid therapy is a feasible alternative. It remains to be seen whether the addition of a leukotriene antagonist is a better alternative than an increase in the dose of inhaled steroids. The clinical significance of the difference between the addition of a long-acting beta-2-agonists and a leukotriene antagonist is difficult to establish. The large individual variation in the response to leukotriene antagonists should also be considered in assessing the benefits. Some patients find their drugs very beneficial to them, whereas a relatively large group of patients have no benefit from their antileukotriene drugs at all. Nor is there any way of predicting who would benefit from leukotriene antagonists.

Should theophylline be added?

The addition of theophylline to the medication of asthma patients who have symptoms in spite of inhaled steroid therapy has been compared with doubling of the dose of steroids (budesonide or beclomethasone) in two separate studies (33,34). The concentration of theophylline in both of the studies is rather low, 8.7–10.1 mg/L on average, i.e. at the lower end of the scale of serum concentrations nowadays considered therapeutic. In both studies the efficacy of the addition of theophylline to the medication corresponded to that of the doubling of the dose of inhaled steroids. The number of adverse effects remained low by using small doses of theophylline. In a third study no such a significant benefit was obtained by adding theophylline to the medication of asthma patients who had symptoms and attended at a general practitioner's consultation (35).

In conclusion

The benefits of addition of a long-acting beta-2-agonist have proven best, and it was shown to be more effective than an increase in the dose of an inhaled steroid in improving the patient's quality of life and the results of pulmonary function tests, and in reducing the symptoms and the need for rescue medication. From a clinical point of view, the benefit to be expected from doubling the dose of an inhaled steroid is rather small, even though it varies individually. Especially in a situation where the patient's problems consist of recurring exacerbations there are

indications that an increase in the dose of an inhaled steroid would be of benefit. The adding of a leukotriene antagonist or a small dose of theophylline to the inhaled steroid therapy has also been found to improve asthma control.

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Summary

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The use of hypnotics on the increase

Sleep disorders are a frequent occurrence and it has become commoner to treat them with hypnotics. In 2000, the total consumption of hypnotics in out- and in-patient care was 49 daily defined doses (DDD) per 1,000 inhabitants, whereas in 1999 the figure totalled 47 (1). In the same year, the sales of hypnotics at wholesale prices in Finland reached almost 68 million FIM, indicating an increase of 7% compared with the previous year.

Hypnotics improve the ability to fall asleep or prolong the duration of sleep. Benzodiazepines and benzodiazepine-like medicinal substances are considered primary drugs in the treatment of sleeplessness. They can in practice, on the basis of their duration of action, be grouped into short-acting, medium-acting and long-acting substances (Table).

In recommended therapeutic doses benzodiazepines are usually well tolerated and safe to use. Their long-term use easily causes dependence, which is why in the treatment of insomnia a short-term use of two weeks is preferred. Tolerance to their effect develops with continuous regular use, and their efficacy is thereby reduced. Furthermore, hypnotics increase the toxicity of alcohol and other CNS drugs.

Grouping of benzodiazepines and similar substances.

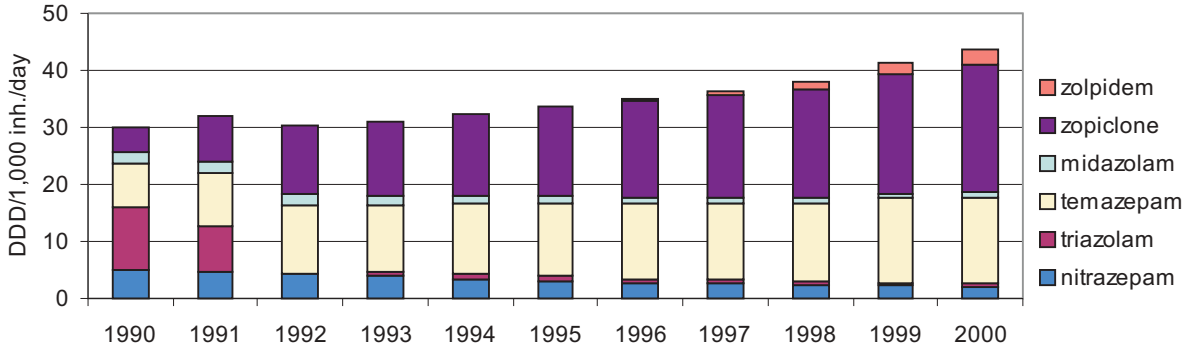
Short-acting	*Medium-acting*	*Long-acting*
Midazolam	*Zopiclon*	*Diazepam*
Triazolam	*Temazepam*	*Chlordiazepoxide*
Zaleplon	*Lorazepam*	*Nitrazepam*
Zolpidem	*Oxazepam*	

In view of their mechanism of action benzodiazepine-related hypnotics such as zopiclone, zolpidem and zaleplon bear a close resemblance to benzodiazepines. They are appropriate mainly for the treatment of difficulty in falling asleep, and seldom cause a state of confusion in the morning. Their sedative effect, development of tolerance and dependence, and toxicity are comparable to those of the benzodiazepines, and consequently, their temporary use is preferred.

The consumption of hypnotics has increased during the 1990s, especially during the latter half of the decade (Fig. 1). Judging by the consumption figures, short-acting hypnotics have been taken into use in the treatment of insomnia; in particular, the consumption of zopiclone and zolpidem has increased. There has been an increase in the use of temazepam, whereas that of nitrazepam has declined. The consumption of triazolam diminished when it was removed from the Finnish market during 1.10.1991–13.1.1993, and the quantity issued for out-patient care was restricted to 20 tablets at one time in 1993. The quantity of midazolam consumed is also dropping.

A review of the amount of hypnotics for out-patient care per package size reveals that the majority of the drugs have been sold in packages sizes of 100 tablets (Fig. 2). The sale of package sizes of 30 tablets has remained stable, and small package sizes are used least of all. In the case of many of the drugs only the 100 tablet packet falls in

Fig. 1. ***Consumption of the most common hypnotics in out-patient care.***



the category entitled to basic refund, which may increase the number of prescriptions for the larger packet. Irrespective of the refund status, the packet size containing 100 tablets is the most cost-efficient one for the user as well because the price per tablet for the small packets has considerably exceeded that for the bigger packages (2).

The consumption of the two drugs sold most, temazepam and zopiclone, also reveals the preference for the largest packet size available on the market (Fig. 3 and 4). In the case of both drugs, the sale of packages containing 100 tablets has increased, and the smallest packages sell very little. In the case of temazepam only the 100 tablet package falls into the basic refund category, and the 100 tablet package of zopiclone is the only size of packet which is eligible for a basic refund irrespective of manufacturer.

According to the recommendations of the National Hypnotics Working Group (3), a course of treatment of insomnia with hypnotics should not exceed 2–4 weeks. Any longer-term use may be a sign of anxiety or other psychiatric disorder associated with insomnia, in which case the need for medical treatment should be reassessed. The preference for large packet sizes indicates that hypnotics are frequently used long-term. Despite the higher price, preference for the small packet sizes could reduce the excess use of hypnotics.

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Translation Mervi Moisander

Fig. 2. ***Consumption of the most common hypnotics per packages in out-patient care.***

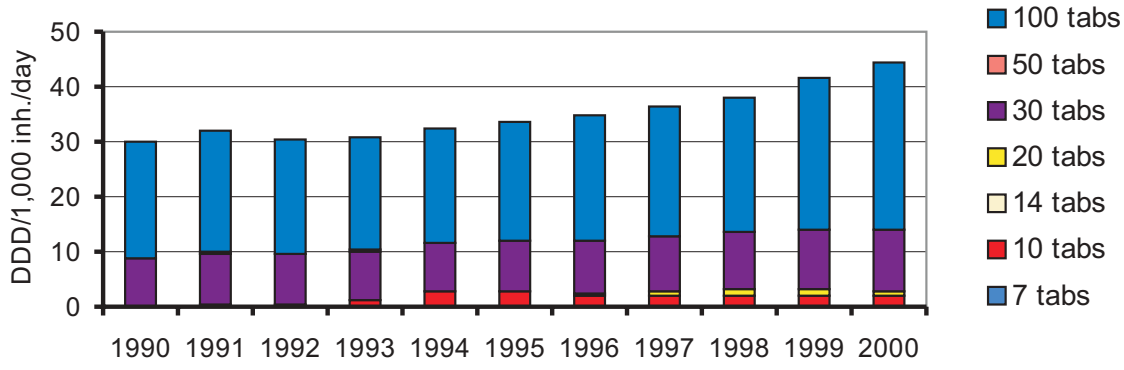

Fig. 3. ***Consumption of temazepam in out-patient care.***

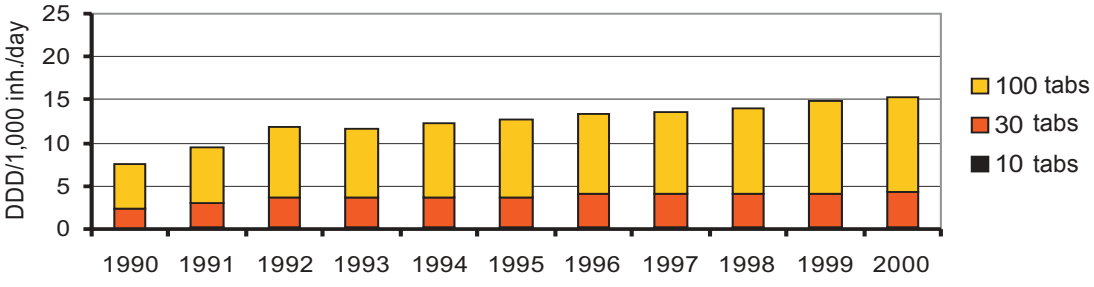

Fig. 4. ***Consumption of zopiclone in out-patient care.***