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Summary

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Summary

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Editorial

Pharmaceutical policy in OECD countries and the competitiveness of the European pharmaceutical industry

Two interesting, international surveys on the pharmaceutical policy and the competitiveness of the pharmaceutical industry were published last year. The report[1] published by the OECD in April 2000 describes recent trends of medicine costs, the pharmaceutical markets and the policies of various OECD countries. In November 2000, the European Commission published a report[2] on its study of competitiveness and the extent of competition within the pharmaceutical industry, especially from a European viewpoint.

These two reports have so far failed to elicit any assessments or debate in Finland. In order to encourage debate and stimulate interest in the subject, it seems appropriate to look at the reports at least superficially. One should bear in mind, though, the element of unreliability associated with the analysis of massive bodies of statistical data extracted at different points in time from various sources.

The OECD report is clearly the more "social" one, due to its broader approach and open acknowledgement of facts. It is admitted in its summary that the purpose of regulating the pharmaceutical sector is to integrate public and private objectives. Here, health and industrial policies are at issue. The report reveals many observations known from before. During the last few decades, medicine costs have accounted for a steadily growing proportion of the gross domestic product, but their share of the total expenditure on health care by the society has remained relatively unchanged (except for in Finland). Further, medicine costs are a less significant factor for affluent countries than for poorer ones; consumers are price-conscious, but physicians prescribing medicines are not; in Finland the reimbursements of medicine costs lag behind those of many other OECD countries, etc.

OECD countries can be divided into two main categories in terms of their policies on pricing and industry. The first category includes countries with strong, research-oriented pharmaceutical industries, where high prices of pharmaceutical innovations are acceptable. The countries in the second category lack strong, research-oriented pharmaceutical industries, their objective being to keep all medicine prices as low as possible.

The table, according to which Finland would support a policy that favours prescribing generic medicinal products, is one of the curiosities of the OECD report. This highlights the need for a source-critical approach.

The survey ordered by the European Commission has a purely industry-political approach. The European pharmaceutical industry is still of major significance for the balance of trade of high-technology and research-intensive industries. In the 1990s, European pharmaceutical industries have not kept pace with the development of the US pharmaceutical industry. Its labour-intensive nature, slow rate of market penetration by innovations, shortcomings in adopting new technologies, and the low level of specialisation are, according to the survey common problems of the European pharmaceutical industry. The lethargy of the national markets in certain European countries after the expiry of patents is mentioned as a major problem. Under such circumstances, prices will not fall, as is likely to happen right away in well-functioning markets.

This survey follows the view often expressed within the pharmaceutical industry, namely that the pharmaceutical distribution systems should operate in more competitive environments. On this occasion, mail order pharmacies are suggested as the remedy.

The two reports have also something in common. They share the view that generics could play a major role in reducing costs and promoting competition. The problem is that promoting the use of generics would entail interfering with prescription, dispensing and cost reimbursement practices.

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[1] Jacobzone, S.: Pharmaceutical policies in OECD countries: Reconciling social and industrial goals. Labour market and social policy – Occasional papers No. 40. DEELSA/ELSA/WD(2000)1.

[2] Gambardella, A., Orsenigo, L., Pammolli, F.: Global competitiveness in pharmaceuticals – A European perspective, November 2000. (http://pharmacos.eudra.org/).

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Medical treatment of glaucoma

Glaucoma is one of the commonest of eye diseases. It is, however, not one individual disease, but a group of diseases comprising in all about 50 different forms of glaucoma. Glaucoma in its most typical form becomes more common with age and is usually a symptom-free and slowly progressive eye disease characterised by destruction of optic neurofibrils and visual field impairment starting from the periphery. The emergence and progress of the disease is generally difficult to detect by the sufferer himself/herself, and the majority of glaucoma cases are uncovered during eye tests performed by ophthalmologists.

Not only intraocular pressure

Excessively elevated intraocular pressure (IOP) is an important risk factor for the disease, but glaucoma also occurs in individuals with normal IOP (< 22 mmHg). In this case the development of the disease has apparently been caused by fluctuating pressure sensitivity due to poor blood supply to the optic nerve and/or poor metabolism of the nerve cells. Pressure measurement alone is not sufficient to determine whether the patient has glaucoma and it is also insufficient in the follow-up of the disease. The most important factor in the diagnosis and treatment of glaucoma is the establishment and investigation of the structural and functional changes in the optic nerve.

Treatment of glaucoma

The treatment of glaucoma consists of drug and laser therapy and surgery. Even though various drugs are claimed to have other effects than reduction of IOP, e.g. effects on the optic circulation or the vitality of the ganglion cells (i.e. neuroprotection), controlled clinical trials to support these effects have not been published. At present, comparison of the effects of antiglaucomatous agents is limited to the assessment of their IOP-lowering effect.

Drug therapy, laser or surgery?

At the start of drug therapy it is important to consider the factors which influence its successful outcome, e.g. patient compliance, need for IOP reduction and the other diseases and medications of the patient. With poor patient compliance and/or acute need for pressure reduction invasive treatment should be considered as primary alternative treatments in association with drug treatment. It is also recommended that physicians establish both for themselves and their patients the principle of maximum drug treatment, which in practice means the most effective feasible treatment with several drug preparations.

Patient compliance

Patient compliance in drug treatment of glaucoma is generally poor. About 50% of study participants do not follow given instructions. Patient compliance can be influenced by the choice of treatment and by focusing on efficacy, number and frequency of administration and adverse effects of the drugs.

Non-responders

Patients receiving drug treatment for glaucoma often include those with very poor response to the drug used. The efficacy of drug treatment is generally considered poor if the reduction in IOP obtained with the drug first used is less than 15% of the baseline pressure level. The drug should be changed for such a patient rather than adding a new preparation to the medication. It should be borne in mind that adding a second or a third drug to the medication may easily curtail the expected reduction in pressure.

Beta blocking agents

Beta blocking agents have been used as eye drops for the treatment of glaucoma since the end of the 1970s. Their popularity grew rapidly due to their good IOP lowering effect and distinctly fewer adverse effects compared with earlier drugs.

The IOP-lowering effect of beta blocking agents is based on the decrease of aqueous humor production by the ciliary body, mainly via β_2-receptor blockage. Besides their efficacy, the advantages of β-blockers also include good topical tolerability. The preparations have, however, systemic adverse effects which focus on e.g. cardiac function (conduction, pulse rate, performance) and blood circulation as well as the respiratory passages (provocation of asthmatic symptoms). The systemic effects of β-blockers can thereby be essentially reduced and a once-daily administration schedule introduced.

Betaxolol is a β_1-selective blocker. Its IOP-lowering effect is poorer than that of timolol. β_1-selectivity has the advantage of a lower risk of pulmonary adverse effects. Betaxolol is one of the drugs which in animal studies have produced neuroprotective effects.

Prostaglandins

Among prostaglandins, the $PGF_{\alpha 2}$-isopropyl ester derivative latanoprost is used for the treatment of glaucoma. Its effect on the eye is based on changes occurring in the intercellular space of the ciliary muscle and the subsequent improvement of uveoscleral aqueous outflow. Latanoprost has a prolonged effect in the eye while it is very quickly inactivated if it enters the circulation. The consequence of this is a long-term effect on the eye and minor systemic adverse effects. Its IOP-lowering effect is the most effective of all among the antiglaucoma drugs now.

In addition to the mild, topical

symptoms of irritation common to all eye drops, growth and thickening of eye lashes and darkening of colour of the iris may occur as adverse effects. Even though the association between latanoprost and the development of iritis and cystic maculopathy has not been proved, it is recommended that its use be avoided as far as possible in patients with a number of risk factors linked with these diseases.

Docosanoids

Docosanoids are, like prostaglandins, lipid transmitters. Unoprostone has been used for the treatment of glaucoma in Japan ever since the mid-1990s. Its mechanism of action still remains unclear but, it seems to be associated with an increase in trabecular aqueous outflows. Unoprostone is administered twice daily and its effect is equal to that of betaxolol.

Carbonic anhydrase inhibitors

The IOP-lowering effect of these drugs is based on inhibition of the epithelial cell carbonic anhydrase enzyme in the ciliary body, which produces the aqueous humor. Frequent systemic adverse effects of acetazolamide and new topical preparations introduced on to the market (dorzolamide, brinzolamide) have reduced its use during recent years. Acetazolamide is the only orally administered antiglaucomatous agent. Its IOP-lowering effect is equal to that of timolol.

Dorzolamide is used especially as combination therapy with timolol in a twice-daily administration schedule. When used alone, it is preferable to administer dorzolamide three times a day to achieve a steady response. Systemic adverse effects with dorzolamide are rare, albeit possible. Topical adverse effects include transient stinging and an unpleasant taste in the mouth, seldom preventing its use. The preparation is not appropriate as a primary drug for patients with corneal endothelium impairment. A recent introduction on to is an eye-drop preparation containing brinzolamide in suspension. Its effect does not essentially differ from that of dorzolamide. The efficacy of topical carbonic anhydrase inhibitors is equal to that of betaxolol.

α_2-adrenergic agonists

The first α_2-adrenergic agonist, clonidine has never attained great popularity ue to relatively poor effect and adverse effects. The new α_2-adrenergic agonists, apraclonidine and brimonidine, have less adverse effects since they do not penetrate the blood-brain barrier so easily.

Apraclonidine is the most appropriate for reducing IOP reactions associated with laser and surgical procedures (1% single-dose pipettes) and for short-term adjuvant treatment of chronic glaucoma patients (0.5% drop bottle). Long-term use is prevented by tachyphylaxis and the frequency of drug allergy. The IOP-lowering effect of apraclonidine is based on prevention of the production of aqueous humor and apparently also on vasoconstriction in vascular membranes with increasing doses. The action is rapid, effective and of short duration.

Brimonidine is the most selective of the α_2-adrenergic agonists. Its effect is based partly on decrease of aqueous humor production in the ciliary body and partly also on increased uveoscleral aqueous outflow on long-term use. The effect of brimonidine is also rapid and relatively short-term. Its maximum effect is actually better than that of timolol, but decreases relatively quickly, becoming distinctly poorer than that of timolol within 12 hours of instillation. Compared to apraclonidine, drug allergy caused by brimonidine is considerably rarer. Dry mouth is a relatively common adverse effect. Similarly to apraclonidine, brimonidine is contraindicated in patients who are treated with MAO inhibitors or drugs affecting the noradrenergic neurotransmission (e.g. tricyclic antidepressants and mianserin).

Adrenergic agonists

The popularity of a prodrug of adrenaline, dipivefrin, has decreased significantly as new antiglaucoma agents have been marketed. Reason for its reduced popularity is the rather low efficacy (particularly in combination therapy), as well as its allergenic propensity and unfavourable effect on any subsequent IOP surgery. Its IOP-lowering effect is based on increased trabecular aqueous outflow.

Cholinergic agonists

Pilocarpine has been used for the treatment of IOP disease for over 100 years. Its effect is based on a structural change in the iridocorneal angle caused by ciliary muscle constriction and subsequent increased outflow. Pilocarpine is characterised by its rapid short-term effect. Its IOP-lowering effect starts within 20 minutes of instillation and lasts for about 4-6 hours. The use of pilocarpine is restricted by the frequent instillations required and characteristic, relatively common topical adverse effects. Pilocarpine has mainly been used as a combination preparation and in the treatment of some glaucoma forms (e.g. narrow angle glaucoma).

Combination preparations

The advantages of combination preparations are manifested mainly by improved patient compliance. Less frequent instillations will also decrease exposure to the excipients of eye drops and reduce the risk of mix-ups of bottles. Treatment with combination preparations is also more cost-effective.

Individual drug therapy

Development in recent years has introduced more alternatives and opportunities in the treatment of glaucoma. It is easier nowadays to tailor the drug treatment to suit each individual patient. Due to the numerous alternatives it is possible to make the treatment for the patient very complicated. Therefore, the common sense is to be followed, and the physician should consider how many eye-drop bottles and what frequency of instillation he/she himself/herself would be prepared to handle to treat his/her own eyes year after year. As an alternative to drug treatment, the physician should also be prepared to consider surgery sufficiently early on in glaucoma.

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Drug development and preclinical toxicity studies

Why are drugs tested on animals?

Preclinical toxicity studies with regard to risk assessment are necessary for the safety of patients. They should always be carried out before the clinical trials of drugs and should be associated with the application for marketing authorisation. The behaviour of the medicinal substance in humans can be predicted on the basis of preclinical pharmacodynamic, toxicodynamic and toxicokinetic studies.

The trials should be carried out on animal models in respect to each issue in question and performed for all new medicinal substances and excipients. The duration of preclinical studies depends on the length of the therapy associated with the clinical trial and on its intended indication. As a rule, the toxicity study prior to clinical trials should last longer than clinical trials on humans. The most important preclinical and clinical guidelines for safety assessment are to be found on the website of the EMEA http://dg3.eudra.org/eudralex/vol-3/home.htm#3b.

Preclinical documentation

In addition to the customary details about animal toxicity, the preclinical documentation attached in support of the application for marketing authorisation should also contain details of all pharmacodynamic, toxicodynamic and toxicokinetic studies, the correct utilisation of which should always be reviewed in each individual case.

In my opinion, accountability in budgeting and time-scale does not provide drug developers with a "window of opportunity" for maximising the utilisation of preclinical information for safety purposes in clinical trials. One reason for this is that the clinical trials are often initiated almost simultaneously with some of the animal studies. Consequently, communication between preclinical and clinical research units, which can be situated on opposite sides of the globe, may remain inadequate.

When carried out correctly, preclinical studies also assist clinical studies in charting the toxicity profile of active agents following the approval of marketing authorisation. They can be compared with the occurrence of adverse effects detected or followed up during clinical use. If, however, an area of toxicity is inadequately studied in animals, clinical studies may not be able to safeguard against the undetected adverse effect.

"Fast track - high throughput"

Even where there is rapid product development, the marketing authorisation of drugs should be based on comprehensive evaluation of the medical risk/benefit ratio. In the expectation of quick financial benefits or scientific feedback, both drug developers and drug authorities have succumbed to "fast track" thinking especially with respect to biotechnology products and gene therapy.

A gene transfer agent used in a gene therapy trial in the USA, an adenovirus vector, caused the death of a patient. In the aftermath of this several oversights in the conduct of the research scheme and its ethical and scientific evaluation by both the FDA and the executives of the study came to light. What is more, the danger in question had already been demonstrated in the preclinical documentation. Are we unwilling to accept a signal from a toxicological study as being valid?

I have often come across such issues in my work in the evaluation of medical research studies. Clinical phase I (single dose studies in a small number of healthy volunteers) and phase III (long-term studies in thousands of patients) since the gradual development of toxicological data is a prerequisite for their inception. In a profit-oriented environment "adverse" signals, particularly those associated with patient safety, draw conspicuously less attention than "high throughput" findings which support and accelerate productization.

Inadequacies in toxicological evaluation are also encountered owing to the neglect of guidelines. For instance, the eyesight of study animals may not be examined, and reference be made to the documentation of some similar agent, often using invalid arguments. Obfuscation may result in the loss of eyesight in patients.

The clinical researcher has a heavy responsibility. The ethical and scientific completion of the whole of

a scientific program is part of the researcher's duty; he/she must also assess the adequacy of the toxicological data with which he/she is prepared to start the study (has the preclinical documentation been supplied for evaluation and approval by the researcher?) and the details of the adverse effects and risks to which the patients have been alerted.

Biotechnology

Animal studies on carcinogenicity are not required in safety documentation of proteins of human derivation (e.g. human insulin) and human peptides produced by biotechnology, unless the product has a direct or obvious stimulating effect on cell division. The extent and level of preclinical documentation for these products are primarily dictated by the quality of the product and methods used for its manufacture. Reference is often made to the lack of appropriate animal models, especially regarding biotechnological products, which is of course regrettably often true. For instance, knock-out or transgenic animal models developed for a specific project are often used in the study of rare diseases. In this case the natural homeostasis of the animal is interfered with, and consequently the result can no longer be completely ascribed to the animal species in question or to humans. The removal of a certain gene from an animal will not guarantee that the disease under study would occur and develop in the animal model in the same way as in humans.

For instance, an extensive international project which investigates the use of genetically engineered animals to force the pace of toxicological evaluation of carcinogenic substances has been extended and become more complicated year after year. The aim was to cut down to a quick 6-month test the research time required for detecting cancerous substances in a two-year animal study on carcinogenicity. In practice, considerably longer research periods have already occurred during the project. Nevertheless, the list of false positives and false negatives with known markers still remains unclear.

The overall economics of the projects are also adversely affected by the high price of acquisition of the genetically engineered animals used.

Concerns associated with gene therapy include are the same as for the traditional drugs, such as the pharmacokinetics and toxicokinetics of the transferred genome and its stability in the target tissue.

GLP

Preclinical studies carried out in connection with patient safety should adhere to the standards of GLP (Good Laboratory Practice). But the guidelines for GLP do not guarantee a high scientific level in the study; the GLP status is only an indication of the method of performing the study. In recent years the world of academic research has been faced with falsification of research results and phantom reports. Unfortunately, examples of the same phenomenon can also be found in drug development. In this respect, evaluation of the GLP status and the entire clinical trial process is a challenge to both drug development projects and the drug supervisory authority.

The predictability and functional value of toxicological research

In recent years, drugs have been withdrawn from the market owing to unexpected adverse effects soon after approval of their marketing authorisation. This may partly follow from the excessively fast development programme and playing-down of risk acknowledgement during development work. In some cases the preclinical documentation has been re-evaluated. It has then transpired that adverse effects occurring at the level of idiosyncrasy (extremely rare cases of severe adverse reactions such as liver damage or anaphylactic reaction without preliminary symptoms) could not be predicted using traditional animal models like rodents. Yet if all the data had been properly utilised, the SPCs (Summary of Product Characteristics) restricted in accordance with preclinical studies, and the marketing correctly focused, there would, in certain cases, have been no need for complete withdrawal of the preparations from the market. In this respect, there is no justification in drug development work for putting preclinical data to one side in favour of market forces.

A sufficiently restricted SPC is always an advantage for a preparation with a new mechanism of action. Carefully guided use of a drug will augment the knowledge of a molecule in a controlled fashion and may grant the substance a "new lease of life".

Preclinical data in drug information

In the Summary of Product Characteristics the preclinical safety data are published in individual sections in only two places: *4.6 Pregnancy and lactation* and *5.3 Preclinical safety data*. Brief details of adverse effects qualitatively established preclinically are published in these sections. In this context the prescribing physician is not able to see the information which has probably determined the clinical research programme and influenced the entire assessment of risk. This aspect of preclinical research may be shown under the headings of sections *4.4 Special warnings and special precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 5.1 Pharmacodynamic properties,* and *5.2 Pharmacokinetic properties*. With this in mind, the real value of emphasising preclinical research in the definition of drug safety is seen as considerably more important than might be expected from the traditional distinction between preclinical and clinical trials.

Literature

http://dg3.eudra.org/eudralex/vol-3/home.htm#3b.

Summary

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Neutropenias caused by drugs

Neutropenia is one of the commonest adverse effects induced by drugs. A large variety of drugs may cause it. It is commonly mild, asymptomatic and detected coincidentally. Severe and fatal adverse blood reactions are fortunately rare.

Because of their mechanism of action some drugs cause dose-dependent neutropenia in all their users. This group of drugs includes cytostatics and eg. interferons. Neutrophil production in the bone-marrow is reduced by the action of the drug, resulting mild anaemia and thrombocytopenia. Neutropenia generally appears 8–14 weeks after the start of administration, but is usually resolved within less than one week. Subsequent exposure to the drug will cause neutropenia within approximately the same period of time as the first exposure.

Numerous drugs periodically and idiosyncratically cause neutropenia. Neutropenia is nevertheless manifested in only a small number of patients and is not generally dose-dependent. It usually occurs suddenly, and re-exposure to the drug causes a quicker and more severe reaction than the first exposure. Neutropenia generally disappears within 7–14 days following withdrawal of the drug. Reactions occurring in the peripheral circulation may resolve a couple of days, whereas with severe bone marrow damage neutropenia may even continue for several weeks.

The most usual mechanism is likely to be an immunological reaction caused by the drug or its metabolites which focuses on either the circulating neutrophils or the stem cells of the bone marrow. Women and the elderly are more likely than other persons to develop drug-induced neutropenia. Genetic factors also apparently influence the predisposition of patients to develop drug-induced neutropenia.

Drugs periodically causing neutropenia

Antipsychotics and antidepressants, especially clozapine, mianserin and phenothiazine, may cause neutropenia. Mirtazapine, fluoxetine and olanzapine have also been reported as causing neutropenia. The risk of neutropenia associated with the use of clozapine is very well known, and blood count monitoring is carried out very extensively. Consequently, clozapine has not caused further fatalities for almost ten years.

Many anti-inflammatory analgesics and antirheumatic drugs cause neutropenia. However, neutropenia can also be associated with the use of prostaglandin inhibitors. Among antirheumatics, neutropenia is associated mostly with the use of penicillamine, sulfasalazine and gold.

Reports on neutropenia associated with antimicrobials have included at least sulphonamides, sulfatrimethoprim, chloramphenicol, beta-lactams, nitrofurantoin and metronidazole. Isolated reports have also been received on quinolones, but the association with the drug remains unclear. With cephalosporins, the dose and the length of therapy are of importance in the development of neutropenia. Neutropenia is often associated unequivocally with large dosages and long-term use.

Among antiepileptics neutropenia has been linked especially with the use of phenytoin and carbamazepine. Isolated cases of neutropenia have also been reported in association with the use of newer antiepileptics (oxcarbazepine, lamotrigine), but the association remains unclear.

The risk of neutropenia is associated with the use of all antithyroids. Among oral antidiabetics the risk is especially associated with the use of sulphonylureas.

Furthermore, the possible risk of neutropenia should be kept in mind when antihistamines and H_2 blockers are used. Individual drugs which cause neutropenia include allopurinol, thiazide diuretics and ticlopidine.

Cases reported during 1996–2000

During 1996–2000, the national register of adverse effects in Finland received 289 reports of cases where leucocytes were adversely affected by various drugs.

Clearly the majority of reports, a total of 115, refer to clozapine. None of the cases were fatal. In the order of frequency of events the subsequent drugs are: mianserin 23, sulfasalazine 16, carbimazole 13, sulfatrimethoprim 13, and a combination of metamizole with pitophenone 9. Fatal adverse effects or effects contributory to death totalled 11. These effects were ascribed to the following drugs: the use of methotrexate was associated with 3 cases, metamizole and allopurinol with 2, whereas mianserin, carbimazole, taxoterine and infliximab have all been reported to have led to one fatality each. Fatal effects or effects contributory to death associated with adverse drug effects on blood totalled slightly less than 30 during the entire 1990s.

However, the reported cases are likely to be only the tip of the iceberg because mild cases of neutropenia will most certainly often go unreported. The vigilance of clinicians is of great importance, especially at the introduction of new drugs on to the market.

Translation Mervi Moisander