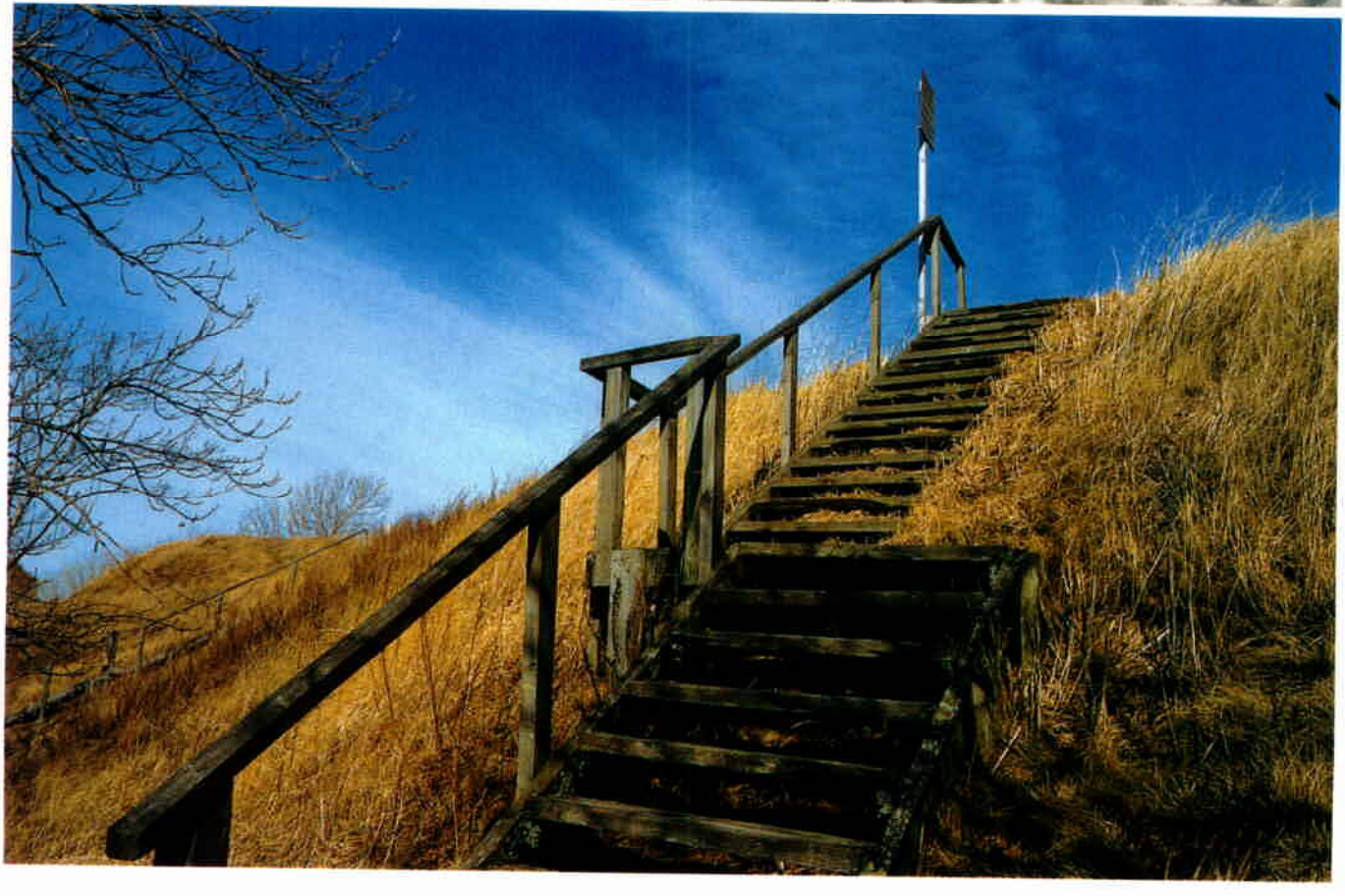
2.2000

TABU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA

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



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Lehden artikkelien otsikot löytyvät aiheittain ryhmiteltynä Lääkelaitoksen kotisivulta ***www.nam.fi*** *kohdassa Julkaisut – TABU. Hakemistossa ovat mukana artikkelien otsikot ensimmäisestä numerosta (1.93) lähtien. Numerot 3.99, 4.99, 5.99, 6.99 ja 1/2000 löytyvät kotisivuilta pdf-muodossa.*

Summary

Erkki Palva
Research Director
Drug Information Centre
National Agency for Medicines

Editorial

Is pharmacovigilance faltering or reaching its goal?

During the past year, many new medicines were withdrawn from the market in Europe due to serious adverse drug reactions (ADR). The recognition of the health hazards of sertindole, tolcapone, trovafloxacin and grepafloxacin, and the ensuing action taken give rise to two issues: Firstly, are medicines placed on the market too early under the present marketing authorisation system, and secondly, have the safety regulations for the medicines placed on the market been drastically tightened?

Is pharmacovigilance activity faltering, and what exactly does it involve? Pharmacovigilance relates to medicines after they have been placed on the market, and covers all the measures taken to elicit signals of health hazards and to analyse such signals, and the action taken to increase drug safety following careful consideration of advantages and disadvantages. The first years on the market are usually the most critical for a medicine in this regard. Prior to marketing authorisation being granted to a new drug, it has been studied in a few thousand patients maximum, and such clinical use has failed to reveal rare ADRs. The use of a medicine in clinical trials is far more controlled than in real-life situations, when problems pertaining to ancillary diseases and drug interactions usually only manifest themselves. All that used to be so even in the past; our knowledge of these matters at the time of granting marketing authorisation is, in fact, greater today than before. Why, then, does it seem that problems are cropping up more often and faster than before?

A part of the phenomenon can be attributable to current global marketing: Significant drug innovations are placed almost simultaneously on the EU and the US markets. This exposes a large number of patients to the new medicine, and that tends to increase the incidence of health hazards or ADRs related to its use. When all ADR reports are effectively and rapidly collected from all markets, the result is a wealth of ADR signals. One of the problems experienced in analysing them is that many signals cannot be proved or disproved merely on the basis of the ADR reports. More information on the basic mechanisms and on comparative epidemiology would often be required. As the signals are becoming more and more voluminous, decisions on safety need to be taken at a time when the safety profile of the medicine is still rapidly changing and imprecise.

Solutions on drug safety within the EU are more and more often taken jointly, regardless of which procedure was followed when marketing authorisation was granted for the drug in question. The advantage of this procedure is that many experts participate in assessing problems of safety, resulting in the criteria underlying the conclusions drawn becoming established, and diverse measures of individual Member States will not arouse concern among the users of the medicine. The diversity of drug therapy traditions and customs in the EU Member States poses a challenge for any efforts to harmonise the measures to be taken.

National ADR registers still play an important role in pharmacovigilance. They form the basic network that transmits new signals of the health hazards associated with medicines. In Finland, this basis has grown strong and solid over three decades, and the activity level in reporting cases to the ADR register is rising. Single observations generate significant signals, insight and suspicion, which makes uncertain, even unusual adverse reactions well worth reporting.

As collecting spontaneous ADR reports is hardly ever enough for a quantitative analysis and closer description of ADRs, other tools and measures are essential. On the one hand, a return to experimental studies of the potential mechanisms behind the reactions observed is needed; on the other hand, epidemiological studies are indicated to determine the incidence and extent of hazard of the ADRs observed. Once the ADR mechanisms, severity of hazards and population groups at risk are better known, removing a medicine from the market will no longer be the only possible avenue open to the authorities. Instead, a solution whereby identifying the high-risk patients, and the use of the medicine by those patients who stand to benefit from it most, may become possible.

Translation Liisa Fellman-Paul

Summary

Raimo Suhonen
Senior Lecturer in Dermatology
Mikkeli Central Hospital

I am going to try an antifungal..

The diagnostics of superficial fungal infections (of the skin, hair and nails) is not easy if the infection is located anywhere but in the lateral toe web. The diagnosis is not easy for a dermatologist, it is even more difficult for a general practitioner, and it is in practice impossible for a pharmacist, so the patient is totally adrift in this respect if he/she decides to treat him/herself. What is the use of OTC antifungals?

Tinea pedis between the toes, or "Athlete's foot", is found in every fourth person, usually in the lateral toe web. It can be treated with OTC drugs, and it may in most cases be cured if the period of treatment is long enough. Plantar type of tinea should be treated effectively to prevent it from spreading to the nails. Among several external antifungals only terbinafine has produced relatively good results in the treatment of tinea pedis on the sole, but the primary treatment for this form of infection should be an internal antifungal. Self-treatment in this case tends to be wasted. The sole of the foot may also have other common skin orders (eczema, psoriasis, pustulosis) where antifungals are ineffective.

A topical antifungal is also effective on tinea cruris (superficial fungal infection of the groin). Eczema or psoriasis in the same area does not respond as well to antifungal treatment. However, they may react favourably to antifungal treatment and to a combination of antifungals and hydrocortisone in particular. A wrong diagnosis may, by coincidence, lead to a favourable result as hydrocortisone has a calming effect on the skin rash and the antifungal gets rid of the topical yeasts, which may play role in the clinical picture.

The body, face and scalp may contract several skin infections which may 'look like fungus' to the layman - whatever it may mean in each case. A real fungal infection (tinea) in these areas is rare, but this does not prevent patients from trying an antifungal first.

The diagnosis is ruined

When the patient eventually arrives for a doctor's appointment it is usually a case of a 'post festum' situation: the patient may well have a fungal infection for which the effect of an OTC drug is not adequate enough, but the drug may have changed the clinical picture and made the infection more difficult to diagnose. Fungal samples would be helpful in the diagnosis. However, an antifungal used on the skin often renders the culture 'incorrectly negative' - it has a smaller effect on direct microscopy (KOH).

Allergy to antifungals is relatively rare, but the development of allergy will naturally depend on the duration of drug therapy. It is likely that the availability of OTC drugs will result in an excessive use of antifungals.

Why do we have OTC antifungals?

The aim of OTC antifungals is probably to lower the treatment threshold, save restricted health care resources and patients' expenses. Correct diagnosis and immediately targeted treatment are, however, more cost-effective than random attempts of treatment. I estimate that antifungals to the value of FIM 25 million of the gross consumption totalling FIM 35 million are used on an incorrect basis. My estimate is based on a study, which found that over 60% of diagnoses made on skin disorders by British GPs were correct. The results of pharmacists and patients remain well below this, as it is rather uncommon for patients to undress at the pharmacist's counter.

In the course of practice, dermatologists have become convinced

The most commonly affected area by tinea is between the toes. Diagnosis between the toes is usually not difficult, and tinea pedis in the toe web can also be treated with OTC antifungals. If symptoms appear on the sole of the foot, present OTC external antifungals are not usually effective enough.

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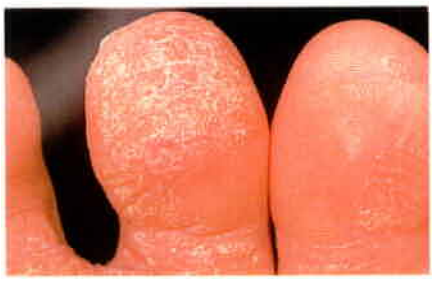
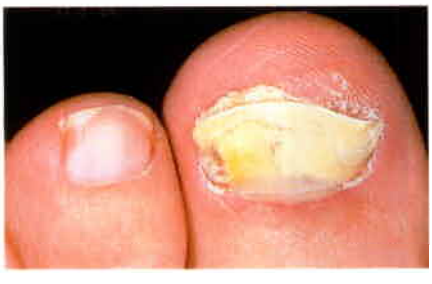
that the most cost-effective and quickest way of treating most skin infections would be to advise patients to make an appointment with a dermatologist directly without trying self-treatment. The conviction is also based on experience on fungal infections, suspected infections and results of self-treatment.



Plantar type of tinea is characterized by the fact that the symptoms may for a long time be exhibited only on one foot. The treatment of this toe with an OTC antifungal before a diagnosis could delay the confirmation of the true diagnosis in the patient. The patient has psoriasis.



Tinea unguium is generally distal, subungual, i.e. it grows under the nail. Its treatment with OTC drugs is useless and would upset fungal examinations. No topical treatment is effective in tinea unguium of this degree.

Erkki Palva
RESEACRH DIRECTOR
Drug Information Centre
Nationa Agency for Medicines

Reports of adverse drug reactions 1999

A total of 750 adverse reactions were reported to NAM in 1999; the number of reports totalled 776, which is a record so far. The number of reports has grown steadily, and the percentage of serious adverse reactions among the reports has at the same time remained constant, i.e. about 40%. (Figure) The reports are evenly distributed amongst various drugs, which is demonstrated by the fact that only fourteen drugs received over ten reports each (Table).

Table. Drugs reported most often in 1999.

Drug	*Number*
Clozapine	*34*
Amoxycillin	*26*
Terbinafine	*23*
Nimesulide	*16*
Atorvastatin	*15*
Mirtazapine	*13*
Sildenafil	*12*
Vigabatrin	*12*
Simvastatin	*11*
Reboxetine	*11*
Sulfa trimethoprim	*10*
Tramadol	*10*
Valproic acid	*10*
Olanzapine	*10*

The table of the most frequent reports on adverse reactions should in no way be considered as a list of the "most harmful" drugs since there are various reasons as to why a drug appears at the top of the list. Many new drugs that are rapidly increasing in use are found on the list; when the aim is to report all adverse reactions of these, the number of reports will naturally be higher than that of reports on many old familiar drugs. The list also includes old drugs that often cause serious adverse effects. The list should primarily be considered as an indicator of safety issues and concerns that are associated with drugs and most frequently discussed. It cannot be used to compare the safety of various drugs.

The list is topped by an atypical neuroleptic, clozapine, the majority of reports on which are associated with neutropenia or agranulocytosis. The adverse effect is exhibited in about 1% of all patients introduced to clozapine therapy. A structurally related agent, olanzapine, appears much safer in this respect; only one of the reports made on it was associated with neutropenia.

The constant position of amoxycillin at the top of the list is due to its wide use, with skin rashes reported as the main adverse effects. The use of terbinafine has primarily resulted in reports of loss of taste and skin reactions, three cases of which were associated with severe erythema multiforme. Among new anti-inflammatory analgesics, nimesulide has resulted in five reports on an increase in liver enzymes including reports mainly on symptoms of the skin and gastrointestinal canal. Reports on statins were most frequently associated with atorvastatin, simvastatin and fluvastatin. Typically, the reported cases with all drugs included myalgia and an increase in

Summary

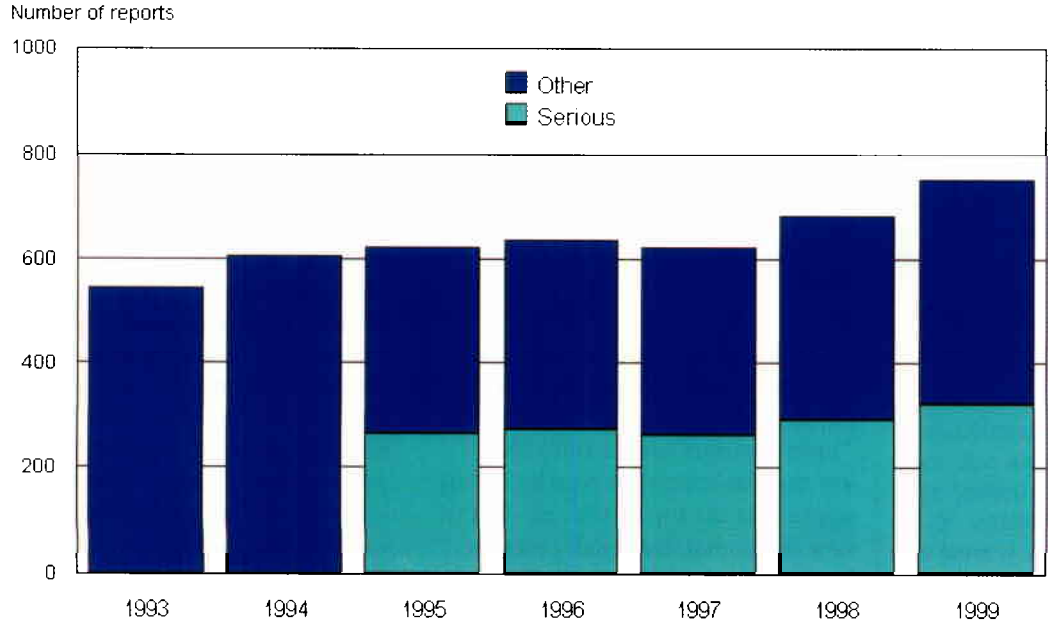
liver enzymes.

Mirtazapine and reboxetine were the most frequently reported drugs among new antidepressants, the adverse reactions evenly cover a large variation of symptoms and findings. Vigabatrin is the most infrequently used drug at the top of the list. It is known to cause narrowing of the field of vision, a 'tunnel vision' in a considerable number of patients, in fact in as many as over a third of patients, and all except one of the 12 reports last year were associated with this. This reflects the fact that the safety follow-up of the use of vigabatrin is considerably improved in respect of visual fields, in particular. The most common reason for reports on tramadol is its effects on the central nervous system causing, for example, nausea, vomiting and convulsions. The profile of reports on valproic acid consists mainly of harmful effects on the liver and blood.

The wide publicity attracted by sildenafil has partly contributed to the active reporting of adverse effects: a total of 11 of 12 reports were associated with a cardiovascular case (7 myocardial infarctions). As this is already a rather common issue among the target group of patients, in view of only these reports, it is difficult to say anything on the possible risk attributable to the drug.

The national registers of reports on adverse reactions continue to form the cornerstone of drug safety procedures, and the success in finding new issues is primarily dependent on the activity of reporters.

Figure. Reports on adverse drug reactions in Finland



Summary

Jussi Holmalahti
DOCTOR OF PHARMACY, CHIEF RESEARCH SPECIALIST

Liisa Turakka
PROFESSOR, HEAD OF DEPARTMENT

Department of Pharmacy
The National Agency for Medicines

Nasal administration of drugs

The nasal mucous membrane is one route for the administration of drugs. It is traditionally used for drugs with a topical effect, such as vasoconstrictive drugs and antihistamines. In recent years, this route of administration has been found appropriate for some new systemically effective drugs (e.g. calcitonin and buserelin). Despite the possibilities offered by nasal mucous membranes as a new route for administering drugs (e.g. proteins and peptides), a number of problems still remain unsolved.

Traditional formulations

Liquid formulations are appropriate in situations where there are no major problems with safety or efficacy, as in the treatment of rhinitis, for example. The administration of nasal drops is reliable for small children where the amount of fluid covers the entire mucous membrane. Liquid administered in the nose in adults runs down the throat and is quickly eliminated. The distribution of liquid preparation has been improved by using squeezable multi- and single-dose containers but the dose is inaccurate when multi-dose containers are used.

Preparations containing propellant

A propellant improves the administration of liquid drugs. Sprays similar to aerosols are the most commonly used formulation in inhaled drugs. Efforts to replace freons in inhalations have begun, but it is premature to predict whether a similar change will take place in nasal preparations. The problems of preparations containing a propellant are linked with the high rate of dispersion and the sensations caused by the propellant on the nasal mucous membranes.

Mechanical devices of administration

The abandoning of freons has speeded up the development of alternative devices. There are a number of single and multi-dose devices available for the administration of liquids and suspensions, emulsions, ointments, and gels.

In the first multi-dose devices, the mechanical pump was connected to a glass drug container. Easily sterilised glass has been replaced with plastic alternatives with superior properties in view of both usability and durability. Properties linked with administration are controlled by three properties of the pump: the volume of drug solution, the dispersion angle of the spray and the drop size of the spray.

The behaviour of the spray is affected by physical properties (viscosity, surface activity, thixotropicity, density) of the drug. Optimum spray for nasal administration contains relatively large size drops to avoid the drug from being transmitted further in the respiratory airways.

A dose meter can also be attached to modern devices. The shelf-life of the drug has been improved with the design of separate structures for the device and the container, and the fact that the drug is prepared for use immediately prior to administration.

Devices with no preservatives

Preservatives have been necessary in conventional mechanical pump devices. During administration, the drug must be replaced by air from the outside to avoid under-pressure forming in the container. It is possible to guarantee the cleanliness of the replacement air either chemically or mechanically in the most recent devices.

Single-dose mechanisms, which work in a similar way as single dose injections, belong to one group that is under development. The drug is packed in a glass ampoule, which releases the drug either with the help of internal or external pressure of the ampoule. This method makes it possible to achieve a very accurate and rapid administration of drug e.g. in emergency situations. The method can also be used in the administration of drugs with a short shelf-life as a lyophilized powder and a solvent can be combined immediately prior to administration.

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New possibilities of nasal administration

Hormones are mentioned as a new group of drugs that can be administered nasally. E.g. nasal administration of estradiol has been studied.

As with inhaled drugs, the aim is to use powders in nasal administration. Several biotechnical drugs, proteins and peptides in particular, keep best in a dry, solid form. Powder-like preparations remain longer on the nasal mucous membranes than soluble ones. The development of powder-like preparations for nasal administration is easier than for inhalation, because the particle size of powders and associated aerodynamic properties are less important in nasal administration.

A group of drugs studied for nasal administration are vaccines, which are usually solutions for injection or lyophilized powders intended for use in solution for injections. The administration of a powder-like vaccine nasally is one alternative to soluble vaccine preparations with a short shelf-life. Compared with injections, one advantage with nasal preparations is also the ease of their use.

The administration of insulin onto the nasal mucous membranes has long been studied as an alternative to subcutaneous injections. The pharmacokinetic profile of insulin in these studies corresponds primarily to an intravenous injection. The administration requires the use of various aids, however, to guarantee effective and steady absorption of the drug.

Translation Mervi Moisander

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