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Summary

Summary

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Requirements concerning tissue and cells to be harmonised in the EU

During the past decade, medical science has paid considerable attention to the use of human tissue and cells, and their product modifications, in treating illness. Medical devices making use of tissue and cells are now used in supplementary procedures to conventional tissue transplants and implants (allografts). Biotechnological methods can be used to manufacture new, innovative products from tissue and cells. This product group also covers products containing the patient's own cells.

Although the range of products on the market is still limited, there is a lot of research and development activity in this field at present. For instance, demineralised bone tissue for orthopaedic applications, and artificial skin based on human cells for treating wounds are now common in clinical use. Tissue engineering has made vascular grafts and aortic valves possible. Combining tissue engineering and cell therapy has resulted in functional pancreatic tissue, etc. These are examples of products soon to emerge from the R & D laboratories to the market.

Increased use of products of human origin, the concern about their quality and safety, and the associated ethical issues, have alerted the European Commission. EU member states have been under heavy pressure to harmonise the major issues. It has resulted in a Draft Directive being issued in June 2002 about imposing standards of quality and safety on the donation, procurement, testing , processing , storage and distribution of human tissue and cells (known as the human tissue directive)[1]. It is proposed that blood and blood products (apart from the stem cells of blood), and human organs, should be excluded from the Draft Directive. Blood and blood products are already regulated by two Directives[2,3] and a recommendation by the Council[4]. In addition, the so-called blood safety directive[5] concerning blood transfusion services is pending. The proposal is also likely to exclude human tissue and cells removed and then implanted in the same patient. Cell therapy products are currently controlled under the Medicinal Products Directive[2].

Concurrently, the Commission has begun to draft a directive on tissue engineering. An open consultation process on an appropriate structure of the Directive is in progress at present. The question is whether to apply the marketing authorisation procedure of medicines, the medical devices conformity assessment procedures, or pick from these what is relevant for, and applicable to, the product range in question. For the past ten years, the industry has urged for the creation of harmonised European requirements. Now the Commission and the authorities in member states are also feeling the need for harmonised regulations in order to ensure patient safety.

A rosy future has been forecast for bioengineering products. There are high expectations for the future of new innovations. Competition between research teams is fierce. The opportunity to prosper by trading in new products seems attractive. In a recent technological review on the medicines control of bioengineering R & D, published by TEKES, The National Technology Agency of Finland, it is claimed that capital would be available for high risks investments, but knowledge about the requirements imposed by the authorities is scant.

The legislators must see to it that national legislation provides for patient safety without loopholes. When drafting Community legislation, one must look ahead, recognise broad entities, and provide for the necessary co-ordination. In Finland, legislation of this kind is drafted by the Ministry of Social Affairs and Health. The National Agency for Medicines assists the Ministry with its expertise. The avalanche of bioengineering products poses new challenges for the National Agency for Medicines; its range of expertise needs to be extended and broadened.

*1 COM/2002/0319 final**
2 2001/83/EC
3 2000/70/EC
4 98/463/EC
5 COM/2000/0816 final

**http://europa.eu.int/eur-lex/*

Translation Liisa Fellman-Paul

Summary

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Suspect an allergy when a rash is worsened by cortisone ointment

Corticosteroids* are widely used anti-inflammatory and immunosuppressive drugs. Their role is still important in the treatment, for instance, of several skin diseases. Problems in the use of corticosteroids are generally to be expected when treatments become long-term or when long-term treatments are being withdrawn.

Reports of hydrocortisone-induced allergy were received for the first time in the 1950s (1). It was nevertheless only admitted in the 1970s that contact allergy caused by corticoids did occur, albeit uncommonly (2). The last two decades have shown that contact allergy caused by corticosteroids is definitely more common than previously thought. An estimated 1–2% of people with persistent rash have been sensitised to one or more corticosteroids (3). Present estimates of incidences vary between 0.5% and 5% (4).

Clinical picture of an allergic reaction

When an undeniable eczema is not cured by a cortisone ointment, but, in the worst scenario, symptoms are exacerbated instead, the physician in charge of treatment will start having doubts about the diagnosis or the efficacy of the ointment, and the patient will lose his confidence in the skills of his physician. The period of illness may be prolonged, because the patient who has become allergic to a steroid is often suffering from a long-term rash already as such, e.g. eczema in situ, and the slowness of cure does not come as a surprise. The symptoms of corticosteroid-induced contact allergy are seldom dramatic, partly because the anti-inflammatory property of steroids may mask the allergic reaction. Consequently a mild corticoid may be replaced with varying success by a more potent one in the hope of improved response to treatment.

If the corticoid responsible for the contact allergy is administered to the patient systemically, it may cause the original rash areas to flare up again or even lead to exanthema and purpura (5-6). Contact allergy to corticosteroids has been reported also in patients who have used corticosteroids by inhalation or as a nasal application, though only to a small extent considering their widespread use (7).

The skin areas typically displaying symptoms include the feet, hands and face. The risk groups may consist of patients suffering, for instance, from atopic, allergic or other persistent eczema and leg ulcers.

Diagnosis presents several pitfalls

With an eczema patient responding poorly to treatment, corticoid-induced contact allergy should be suspected early on. In Finland contact allergies are studied with epicutaneous (patch) tests (8). Study of allergies is nevertheless constantly undergoing change. Discussion is aroused, e.g., by issues relating to the corticoid concentration and the ointment in which it should be tested (9). False positive and negative reactions may also cause headaches. The former reactions might at least be provoked by response to the medium, and the latter by the above-mentioned anti-inflammatory effect of the steroids, the physiochemical properties of the test substance, poor mixing with the ointment, insufficient penetration of the skin, inadequate concentration, degradation of the corticoid during storage, its vasoconstrictive property (especially on the first test reading) etc. (10). Test responses to steroids anyway do not completely resemble typical epicutaneous reactions. The absorption of a corticosteroid ointment by healthy skin tested on the back is also poorer than by a skin area which is being treated, and consequently the reactions seen with use of the ointment will not necessarily be seen in a test situation.

What is tested and where?

As the proportion of incidences of steroid-induced allergies among contact allergies exceeded 1%, tixocortol pivalate and budesonide have been incorporated into the basic series of epicutaneous tests at the dermatology units of the university hospitals and the Institute of Occupational Health in Finland (8). Tixocortol pivalate has been chosen to represent hydrocortisone-induced reactions because it works better in test situations and cross-reacts with hydrocortisone. Tixocortol pivalate

** Corticosteroids, steroids and corticoids here mean glucocorticoids.*

is tested as a 1.0% and budesonide as a 0.1% ointment with petroleum jelly. Most of the corticosteroid-induced allergies are detected by hydrocortisone or tixocortol pivalate and budesonide (11), and these are recommended in Europe-wide standardised epicutaneous test series (12). A late reading (6th–8th day) is important: without it, as many as a third of corticosteroid-induced contact allergies will go undetected (13).

Individual, tailor-made arrangements of the tests regarding the relevant area and case according to the prescribing practice of corticosteroids and the patient's customary usage are recommended in cases difficult to solve (14). If the patient exhibits an allergic reaction to tixocortol pivalate or budesonide, a corticosteroid test series is nevertheless recommended to be carried out, because a large number of patients become allergic to several corticoids while their long-term rash is being treated with various preparations. As the penetration of the steroid in epicutaneous testing may be inadequate and the test result is about to become falsely negative, an intracutaneous test is often also carried out, which involves the injection of an appropriately diluted substance into the skin of the forearm followed by a reading after 48 hours (15).

Testing of corticosteroid-induced allergies is a finely tuned activity which requires high expertise and long-term experience and should consequently be assigned to an especially dedicated allergy testing laboratory or a specialist unit.

The test applied, ROAT (repeated open application test), is an easy-to-use practical test method which reflects the clinical response of the corticoid used better than an epicutaneous test does. The ointment is applied to the inside of the forearm until a reaction is obtained or for a maximum period of one week. A large number of patients exhibiting a reaction in the epicutaneous tests will also react in the test analogous to use, which can be used as a complementary method (16).

Cross-reactions

Corticosteroids may cause cross-allergy: patients were detected as having allergic test reactions to steroids to which they had never been exposed. Clinical studies and studies based on molecular structures have resulted in categorisation in four different groups in accordance with their allergenic properties (17). Cross-reactions are much more common between corticoids with a closely similar structure and of the same group, than between those belonging to different structural groups. The structure of budesonide is special compared to that of other corticoids, and reactions to it in an epicutaneous test may indicate allergy to corticoids even of two quite different groups. It is suggested that halogenated steroids would cause fewer contact allergies than non-halogenated ones, the likely reason being that the amount of potent halogenated steroid required is smaller, in which case the amount of antigens is also smaller and consequently also the risk of developing an allergy (18).

What follows after the tests?

In the optimum cases the patient's poor healing tendency or exacerbation of the rash will be clarified by adequately extensive allergy tests. There is a great likelihood that the tests will either confirm or exclude a contact allergy. The cause of the problem is often a preservative contained in the ointment or an antimicrobial ingredient or something similar, and the corticoid proves to be innocent. An appropriate therapy should be found for the patient after testing in order to control the original skin problem. Thorough patient guidelines are important; these should contain in addition written information about inappropriate (and cross-reacting) corticosteroids as well as appropriate ones. A list of trade names of all synonymous preparations available on the market will be of tremendous benefit for the patient's subsequent self-treatment.

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Statins and muscular adverse drug reactions

Statins are HMG-CoA-reductase inhibitors with an inhibiting effect on cholesterol synthesis by the liver cells and an accelerating effect on LDL-receptor synthesis, causing a reduction in the plasma LDL-cholesterol concentration.

Clinical studies have shown mild elevations of serum creatine kinase (S-CK) at most in a couple of percent of healthy volunteers.

Once statins became more widely used, myopathies were occasionally found to occur in patients during treatment. Symptoms may be manifested as muscular pain, tenderness or weakness, not necessarily associated with an increased creatine kinase (CK) level, or myositis. In rhabdomyolysis, the muscular symptoms are severe, the CK level is over 10 times higher than the maximum baseline level, and the rising serum creatinine level is a sign of impaired renal function. Rhabdomyolysis may become life-threatening, especially if associated with renal necrosis.

The first statin was introduced on to the Finnish market in 1988. According to the drug reimbursement statistics of the Social Insurance Institution, a total of 260,000 patients obtained refunds for statins last year. The wholesale consumption of statins is shown in Figure 1. Until the end of 2001, estimated cumulative exposure to lovastatin is 182,000 patient years, to simvastatin 282,000, to fluvastatin 73,000, to pravastatin 49,000, to atorvastatin 168,000, and to cerivastatin 3,000 patient-years.

Statin-associated reports

Since 1988 up until the end of August 2002, the National ADR Register received in total 242 reports of adverse reactions of statins (Fig. 2).

A total of 106 muscular reactions were reported in 79 patients. Any one patient may have exhibited more than one symptom. The estimated reporting frequency of statin-associated ADRs has been about 1:8,000 and of myopathies 1:19,000 recipients.

Rhabdomyolysis

Rhabdomyolysis was reported in eight cases (Table 1). A half of these patients needed intensive care treatment. All patients were recovered.

Most patients had contributing disorders and drug treatments. The dose of simvastatin had been doubled in three patients before manifestation of rhabdomyolysis. In a patient administering long-term lovastatin rhabdomyolysis appeared in two weeks from the start of itraconazole therapy.

Other muscle reactions

The ADR Register had during the above period received 32 reports on neurological adverse reactions which included two cases of sensorymotor polyneuropathy in patients on atorvastatin therapy, diagnosed and verified by an electroneuromyographical examination. In one case the symptoms and signs were directed towards the lower limbs and were mild and reversible; in the other they were directed towards the upper limbs, were severe, and were responsible for permanent muscular atrophy and impaired function of the hands.

Figure 1. Consumption of statins in Finland 1990–2001

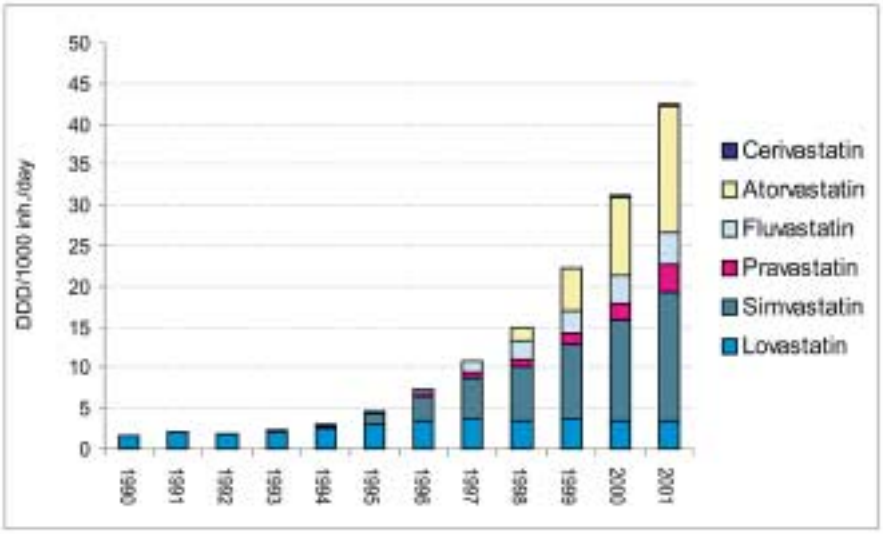

Figure 2. Statin-associated adverse reactions in Finland 1988–31.8.2002

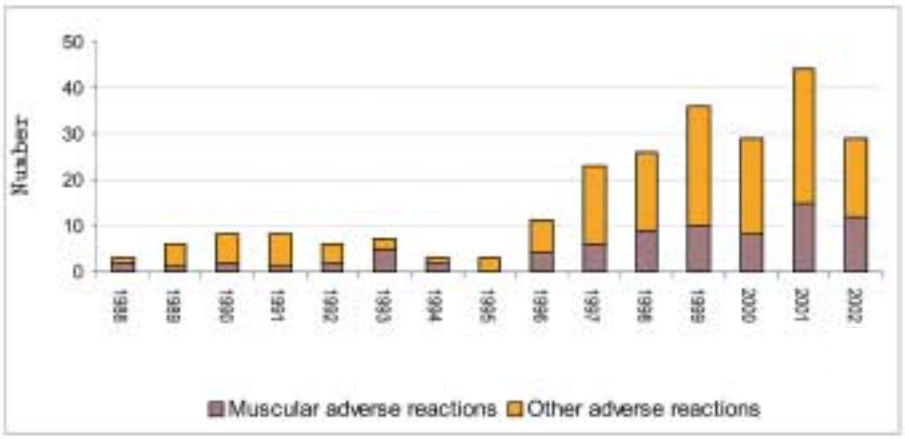

Table 1. Statin-associated rhabdomyolysis in Finland 1988–31.8.2002

Year	Statin and daily dose	Interactive drug	Age and sex of patient
2001	Simvastatin 40 mg	None	68-year-old female
2002	Simvastatin 80 mg*	Macrolide	50-year-old male
2001	Simvastatin 80 mg*	Gemfibrozil	55-year-old female
2000	Simvastatin 80 mg*	Ciclosporin	52-year-old male
2001	Simvastatin 80 mg	Fluvoxamine	51-year-old female
1996	Lovastatin 80 mg	Itraconazole	54-year-old female
1998	Pravastatin 20 mg	Bezafibrate	66-year-old female
2001	Cerivastatin 300 microg	None	54-year-old male

** The dose had been doubled*

The EU CPMP Pharmacovigilance Working Party recommends the measuring of S-CK prior to commencement of statin therapy in the following cases where the patient is increasingly exposed to rhabdomyolysis

- *Renal impairment*
- *Hypothyroidism*
- *Personal or familial history of hereditary muscular disorders*
- *Previous history of either statin or fibrate-induced muscular toxicity*
- *Alcohol abuse*
- *In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.*

In these cases, the risks involved should always be weighed against the benefit of the treatment, and the patient's clinical status should be closely monitored.

If on checking the S-CK baseline level exceeds the five-fold maximum reference value, the introduction of statin therapy is not recommended.

Whilst on treatment

The S-CK level should always be measured if myalgia, weakness or muscle cramps occur during treatment. Should the S-CK level exceed the five-fold maximum reference value, statin therapy should be discontinued. If the muscular symptoms are clinically severe, statin therapy should be discontinued despite only slightly elevated S-CK levels.

If the muscular symptoms disappear and the S-CK level returns to normal, it may after some time be considered, at the lowest possible dose and with close monitoring of the patient.

Factors predisposing to myopathy

Well-known risk factors for statin-associated adverse muscular reactions include high doses of statins, advanced age, chronic renal failure, other muscular disease, multi-drug therapy and the postoperative state. The lipophilic property of statins is under discussion. The safety of use of different statins has not been studied in this context. The differences in statin-associated myotoxicity can in several cases be explained by varying drug-metabolising liver enzymes, cytochrome-P450. The metabolism of simvastatin, atorvastatin and lovastatin is mainly mediated by CYP3A4. The clinically important inhibitors of CYP3A4-mediated metabolism include, among others, cyclosporin, itraconazole, ketoconazole, diltiazem, verapamil, nifedipine, erythromycin, clarithromycin, and several anti-HIV drugs.
As a result of such interaction, the clearance of the above statin may be reduced and its plasma concentration may reach toxic levels. Abundant intake of grapefruit juice and alcohol may cause a similar harmful interaction. Many CYP3A4 inhibitors also are substrates or inhibitors of P-glycoprotein which may contribute to interaction. Fluvastatin metabolism is mediated by CYP2C9. CYP system does not mediate pravastatin metabolism.

The risk of myopathy increases also with concurrent use of fibrates with statins.

Conclusions

In general, myotoxicity is a rare adverse reaction. The life-threatening rhabdomyolysis is most probably a very rare and dose-dependent class effect of statins, in which also interactions may play a big role.

In order to avoid the statin-associated adverse effects, individual dosage should carefully be considered, and the risk of interactions between drugs should be noticed.

When interpreting this data careful consideration is recommended because the present material of ADRs has been obtained by the regulatory authority as spontaneous reports from physicians. The data can not be used for comparison of safety of various statins.

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Pharmaceutical advertising in professional journals for medical doctors

Information on prescription drugs is obtained by medical doctors in the form of pharmaceutical presentations and as mail sent to their home addresses, but the vast majority of it comes as advertisements published in the professional journals. The doctor's first source of information about a newly introduced drug is often a pharmaceutical advertisement.

The marketing of pharmaceuticals in Finland is supervised by the National Agency for Medicines. Pharma Industry Finland (PIF) also supplies guidelines for pharmaceutical marketing (1), which the member organisations have agreed to follow.

According to a regulation "marketing material targeted at health care personnel should, for instance, always contain the essential details which in accordance with the summary of product characteristics (SPC) are related to the indications and recommendations for use of the preparation, including its efficacy and safety of use" (2). The material should also indicate the date on which the leaflet was drawn up or renewed. According to the guidelines for pharmaceutical marketing, the marketing of drugs targeted at health care personnel must be up-to-date and in accordance with the SPC concerned and should contain all relevant information necessary for the prescription of the drug. The details given concerning the drug should also be clear and easy to understand (1).

Considering the above regulations and guidelines and the fact that about one in every ten medical doctors in primary health care relies on the advertisements in professional journals as a source of information, one would think that drug advertisements were unambiguous and complete information packets as far as their contents are concerned. This review was aimed at finding out whether this would be the case: what information do the advertisements reveal and how well does it comply with the information given in the SPCs?

Material and methods

The material used consisted of pharmaceutical advertisements in the medical journals, Lääketieteellinen Aikakauskirja Duodecim and the Finnish Medical Journal (Suomen Lääkärilehti), issues of April and May 2002. The total number of issues of the journals was 12, out of which 8 were of the Finnish Medical Journal. The advertisements numbered 94 in all. The majority of these (87) were advertisements of prescription only medicines. Some of these (7 in all) were advertisements of drugs which were available without prescription in their smallest package format, while the larger formats were only available on prescription.

Seven of the advertisements were divided into two, so that a section of them, the text relating to the SPC, was to be found elsewhere in the journal. Four of these advertisements referred to the fact that information on the SPC would be elsewhere in the journal, and one of them included the page number. In three cases the continuation of the advertisement was not referred to at all, and so they were interpreted individually as separate advertisements.

Several advertisements included different forms and potencies for the same drug. They have in this review been treated as one advertisement. Advertisements of OTC drugs and reminders of advertisements were excluded from the review. According to a regulation of the National Agency for Medicines, a reminder of an advertisement may only refer to the name of the drug, or the name and the marketing authorisation holder (2).

The advertising texts were compared with the texts of the SPCs. The following items were compared: the medicinal substance/substances, indications, contraindications, interactions, adverse effects, special warnings and use during pregnancy and lactation. Whether these items had been referred to in the advertisements was checked, and if they had been, to what extent. Whether the advertisement contained the date (month and year) of the preparation of the material or the date of the latest renewal was also checked. A closer examination was carried out on advertisements with discrepancies in the above information. Details on packaging, price and references were not studied in this review.

Results

The number of companies advertising their products was 28. Not a single advertisement stated that the drug was safe to use or that it did not have adverse effects or that its use was not associated with a risk of

Table 1. The number and proportion of the items mentioned in the SPCs (SPC) and advertisements (A); all or the most common ones are mentioned

Items mentioned	n	SPC/SPC (%)	n	A/SPC (%)	all mentioned (%)	most common ones mentioned (%)
The medicinal substance	94	100	91	97		
Indications	94	100	94	100	93	7
Contraindications	94	100	90	96	86	14
Interactions	86	91	49	57	41	59
Adverse reactions	93	99	76	82	12	88
Special warnings	93	99	57	61		
Pregnancy and lactation	87	93	43	49		
Date			5	5		

dependency. The name of the drug was missing in three advertisements (Table 1). One of them mentioned the relevant group of medicinal substances but did not reveal the name of the drug. In two other advertisements the name of the active substance was indirectly obvious from the name of the preparation, but was not explicitly mentioned. Furthermore, the name of the medicinal substance in one advertisement was visible only on the picture of the drug package.

Indications

The wording on the factual contents and on the indications in most of the advertisements in the review were the same as in the relevant SPCs. Seven advertisements had definite defects or mistakes in the reference to the indications (Table 2). In two of these advertisements the indications for children and adults were different, but this was not disclosed. In three advertisements the references to the indications were excessively general: more accurate information (e.g. for whom and in what circumstances the drug would be indicated) was absent.

Essential information relating to administration was missing in two advertisements. In one of the advertisements (for an antibiotic) a whole range of infections were referred to as indications without stating any restrictions for use. In the other advertisement with definite discrepancies in the content of information, the indications were not stated clearly; instead, the advertisement emphasised the degree of prophylactic effect the drug had against certain diseases.

Contraindications

All the SPCs referred to some contraindications. In about 86% of the advertisements all the contraindications were listed. Only the most common ones were mentioned in 14% of the advertisements (Table 1). References to contraindications were missing altogether in about 4% of the advertisements (Table 2). As a matter of fact, three of these SPCs mentioned only hypersensitivity as a contraindication, and consequently only one advertisement lacked actual reference to contraindications.

Interactions

The SPCs of seven drugs did not mention a single interaction. The most general interactions were mentioned in about a fifth of all the advertisements, and all of the interactions in about a third of them (Table 1).

References to interactions were missing altogether in about a half of the advertisements. According to nearly all of these SPCs, interactions were clinically possible, and consequently, the most common or most important ones should have been mentioned in the advertising material.

Adverse effects

Nine of the advertisements detailed all the adverse reactions mentioned in the SPCs. Over a half of the advertisements detailed the most common adverse effects (Table 1), and a third of these also mentioned some rarer adverse effects.

No adverse reactions at all were mentioned in 19% of the advertisements even though the SPCs of all of these drugs did describe some (Table 2). In addition, no adverse effects were disclosed in one advert, but, it being for an insulin, the borderline between adverse effects and warnings is very difficult to determine. Among the advertisements without any mention of adverse effects, five had covered them with a general comment such as "adverse effects are similar to those caused by a placebo", or "adverse effects are generally mild". One advertisement referred to general adverse effects found in similar drugs: "the adverse reactions reported were usually related to the pharmacological effects of beta-blockers". The SPCs of all these drugs described adverse effects which, according to regulations, should have been disclosed in the advertising material.

The style of the advertisements lacking information on adverse effects was conspicuous without being particularly informative. One advertisement, for instance, described how well the risks of various diseases were prevented by the drug, but without conveying the information contained in the SPC.

Special warnings

Over a half of the advertisements listed special warnings (Table 1). One of the drug advertisements stated that the warnings could be looked up in the Pharmaca Fennica. All the drugs with no mention of special warnings in their advertising listed some warnings in their SPCs. Nearly all of these warnings were associated with adverse effects or diseases in connection with which the drug should be used. About a half of these also contained instructions or advice on the monitoring of

Table 2. Missing, or partially missing items of importance with regard to use and safety

	Missing	%
Indications	*Partly*	*7*
Contraindications	*Totally*	*4*
Adverse reactions	*Totally*	*19*
Special warnings	*Totally*	*39*

the patient's condition or of laboratory values.

Use during pregnancy and lactation
Use during pregnancy and lactation had been mentioned in about half the advertisements (Table 1). In all of these cases, according to the SPC, the drug is either contraindicated during pregnancy or lactation, or should only be used if absolutely necessary, or the use of the drug had not been studied, and so it was advised that it should not be used. Among the advertisements with no mention of pregnancy or lactation, six stated in their SPCs that there were no obstacles to using the drug under such conditions, or that the issue was irrelevant (e.g. in relation to drugs for treating prostatic disease).

Date
Only five percent of the advertisements clearly stated the date when they were drawn up or their details reviewed (Table 1). In about 40% of them the date was placed on the margin of the advertisement either as such or as part of a code. 57% of the advertisements lacked a date altogether.

Conclusions

In general, nearly all essential information with regard to the correct and safe use of the drug was well detailed. The text containing the drug information was nevertheless given in small print in nearly all of the advertisements, and was very difficult to read. It gave the impression that the texts were intended for reading by young people only and in excellent light. The picture often covered most of the advertising space, which raises the inevitable question about the purpose: is it the impression produced by the advertisement or the information contained in it?

Those advertisements where the text of the SPC was to be found elsewhere in the journal were misleading, especially if there was no connection between the two parts of the advertisement. In such cases it would be easy for the reader only to notice the larger and more conspicuous part of the advertisement, in which case the information received from the advertisement will remain incomplete or be lacking altogether.

About a half of the advertisements did not include any warnings whatsoever, and about 19% of them did not list any adverse effects at all (Table 2). It is very difficult to assess which of the warnings or mentions of adverse effects are essential and ought therefore to be included in the advertising. Should, for instance, rare adverse effects be included, and if so, should all of them be mentioned? If only some were selected, on what basis should it be done?

The situation has fortunately improved considerably since 1998. According to a review done at the time, adverse effects were missing in 89%, contraindications in 73% and special warnings in 86% of the advertisements (3). According to a Finnish review done in 2000, for instance, adverse effects were no longer missing in more than only a half of the adverts. There has been no change in the situation for the last two years, however: similar important information is still missing. As Paul stated in his review, it is unlikely that the absence of safety data will cause any major adverse effects, because physicians will hardly prescribe drugs to their patients based on drug advertisements alone.

It is required by the regulation on pharmaceutical advertising that the information on the drug obtained by the reader of the advertisement should be adequate for forming an opinion on its therapeutic effect (2). Based on the perception of this review, it cannot be concluded that this requirement is fulfilled completely. Even though the majority of readers will scan the advertisements quickly, the importance of advertising as a source of information should not be undervalued. Correctly used, pharmaceutical advertising is an excellent channel for providing circumstantial information on drugs for the prescribing physician.

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