



Rauhallista joulua ja onnellista uutta vuotta 2009

God jul och gott nytt år 2009

Season's greetings and best wishes for the new year 2009

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The need for digestibility in the pharmaceutical field

Everyone knows how important moderation is in eating and drinking at Christmas time. Enjoying festive delicacies can otherwise lead to bloating and indigestion. Restraint must similarly be observed in implementing pharmaceutical reforms, otherwise the pharmaceutical field will not be able to swallow them.

Many significant pharmaceutical reform projects have been overshadowed by discussions relating to organisational matters. Projects need to be implemented purposefully, but presence of mind and forethought must not be neglected. Management and co-ordination of the whole is essential. There are also risks involved in trying to do everything at the same time.

The introduction of electronic prescriptions, which has been postponed for many years, is now imminent – it is set to take place in 2011. The relevant authorities and players in this area are currently making preparations. When patients and professionals are granted access to patients' medical histories and details of all prescriptions, this will present an entirely new situation for patients, doctors and pharmacies. The prescription system and the drug supply chain will change, methods for preventing overlapping medications and incompatibilities will improve, the possibilities for carrying out research into drug use will be developed, and counterfeit prescriptions will be encountered less frequently. It must be ensured that final details do not prove a stumbling block, and that the expected benefits of electronic prescriptions are indeed achieved. This project should signal the start of a new era.

The reference price reform was dominated by the debate on pharmaceutical patents. There has been little discussion about any of the other effects of the reform, such as the increased need for patients to receive information at the doctor's surgery or in the pharmacy. Even at this stage of the prescription process, the patient should be made aware of the basis on which the reimbursement will be calculated in the pharmacy. This will pose a challenge both for

doctors and for pharmaceutical staff in the pharmacies. The reform also poses financial challenges, especially for pharmaceutical companies, pharmaceutical wholesalers and pharmacies. Competition in the pharmaceutical industry is becoming ever tougher. All activities need to be economically efficient, but players in this sector are also expected to display a high level of professionalism and skill in managing their responsibilities. Is this yet another Christmas nut that needs to be cracked?

In the autumn, two significant draft laws prepared by NAM were sent out by the Ministry of Social Affairs and Health to players in the fields of pharmaceuticals and medical devices, to allow them to submit a statement. In addition to safeguarding pharmaceutical services in the outlying districts, amendments to the Medical Act should also ensure the introduction of online pharmacy services, improved mechanical dosage distribution, more restrictive measures for advertising of medicines, and increased transparency. The pace of progress of the proposals will become clear in the spring, but in any case the proposals must be faced. Any delay in the reforms will lead to an accumulation of problems in the pharmaceutical sector.

As regards medical devices, NAM's proposal involves not only improving patient safety, but also a reform of all present legislation. Enterprises operating in the field, professional users, health care provision units and the regulatory authorities must each accept their obligations and responsibilities. Collaboration within the EU on the regulation of medical devices further increases the interface synergy with pharmaceutical regulation.

And the EU has some goodies of its own up its sleeve. The expected proposals for directives on pharmacovigilance, drug information and the prevention of drug counterfeits will provide plenty of issues for us to digest next Christmas, too.

Despite the pace of the reforms, on behalf of NAM I have the pleasure of wishing all readers a peaceful Christmas time.

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Inadequate discussion of adverse events in drug presentations in Finland

In 2007 the National Agency for Medicines drew up a recommendation for quality criteria to be applied to drug presentations to assess the factual content of pharmaceutical marketing (1). The question of whether these recommendations were successfully introduced into practice was discussed in collaboration with the Centre for Pharmacotherapy Development ROHTO in the spring of 2008. The results of the survey are based on assessments made by 17 general practitioners which were focussed on the factual content and quality of the drug presentations arranged at their surgeries. The survey covered 83 drug presentations and revealed the details of the extent to which the data made available at these presentations corresponded with the information contained in the summaries of product characteristics and with the need that doctors have for information.

For pharmaceutical companies, drug presentations constitute a significant part of the company's marketing of prescription drugs to the medical professionals who are entrusted with prescribing and delivering drugs to the public. A pharmaceutical representative gives an average of 3 to 5 presentations a day. Doctors participate in 2 to 3 one-to-one drug presentations on average per month and in 4 to 5 group presentations per month (3). For doctors, drug presentations at their best provide quality and up-to-date information about drugs and drug treatments as a whole (1, 2). Drug presentations will decrease in numbers in the future (4). The number of product specialists and drug firm representatives has decreased by 17% in the last three years (3).

Background

We set out by establishing whether the information given orally at drug presentations has been appropriate as regards the quality requirements stipulated for these presentations.

Conclusions

The results of the survey show that slightly more than half (60%) of the drug presentations held at health care centres comply well with the recommendations for quality criteria relating to SPCs, price information and other written material. The results support the impression that drug presentations held during working hours are appropriate in the main, but in presentations of a short duration (40% of the presentations last less than 10 minutes) it appears that the products are not covered as fully as possible, but instead, the drug firm representative leaves background material for the doctor to browse through, making a mention of clinical trials, and instead of a long presentation the representative also mentions the price but makes no price comparisons.

Clinical drug trials are very often referred to, in as many as 94% of the presentations. Therapeutic indications for the products discussed at the presentations almost always corresponded to the information contained in the SPCs. According to experts at ROHTO, the therapeutic indications for products had clearly been expanded in four, and possibly in twelve of the presentations, out of the total of 83 assessed.

Details of the safe use of drugs should be focussed on more during drug presentations. Adverse reactions were only described on 19 occasions in

the presentations assessed. Drug interactions or contraindications were discussed only in 10 presentations, and other issues pertaining to safe use of the drug were mentioned in only 32 of the presentations.

The results of this survey are similar to those disclosed by other surveys of factual content in drug presentations in Finland and other countries (6–14). Several surveys have maintained that drug presentations focus mainly on the positive issues and advantages in comparison with other drugs and alternative therapies. Drug safety issues, adverse reactions and/or interactions are too infrequently discussed at the presentations (6–10, 13).

The survey material is considered a reliable assessment of the quality of drug presentations held in the spring of 2008. According to this survey, the quality and informational content of drug presentations can be improved by providing more details about the significance of the drug as a whole in comparison with other forms of therapy, and by adding further details about the product's adverse effects and its interactions and other issues associated with safe use. Presentations should fulfil the doctors' need for information, for example by providing more information about the epidemiological relevance of the product, current treatment recommendations, and the cost-effectiveness of medicinal products. Of the information provided at drug presentations in Finland in general, 94% corresponded to the content of the SPC of the particular drug, omitting nevertheless a significant amount of information. In 42 of the presentations in the survey no adequate details of the drug safety issues were given.

Literature see page 16

Vitamin D – Southern hormone and Northern vitamin

One of the most remarkable advances of medical sciences in the early 20th century was the cure of rickets and osteomalacia by vitamin D. About half a century later it was evident that vitamin D actually was an endogenous hormone that in the North was needed as a food supplement during the winter months. The active vitamin D, calcitriol is a hormone produced by the kidney. Its previtamin, cholecalciferol (D₃), is synthesized in the skin via the photolytic activity of UVB-radiation. D₃ is then transported protein bound into liver to be hydroxylated to calcidiol (25(OH)-D), which is the substrate for another hydroxylation in the kidney to produce the final product calcitriol (1,25(OH)₂-D).

Now, 200 years after the first documented use of cod liver oil to cure rickets and 100 years after discovery of its active ingredient, the effects of vitamin D have proved to be much more diverse than just supporting homeostasis of the bone. Calcitriol modulates via its nuclear receptor the expression of hundreds of genes related to its own metabolism, immune response and cell

growth. Furthermore, acute effects such as stimulation of calcium transport appear to be mediated via a cell membrane receptor of vitamin D.

The non-skeletal health benefits of vitamin D are related to prevention of hypertension, cancer and autoimmune diseases. Since the present evidence is mainly epidemiological, more long lasting randomized studies are needed to substantiate the initial findings and to define optimal plasma concentration of calcidiol 25(OH)-D, which is used to measure the vitamin D balance. Gaining of the health effects of vitamin D probably requires higher plasma levels than needed to prevent bone disease. Today we know that at a concentration of less than 10 nmol/l of calcidiol the production of the active vitamin calcitriol decreases. To prevent rickets a level of about 20 nmol/l is needed. Plasma concentrations of more than 40 nmol/l are considered "normal" although the people of southern countries appear to have concentrations between 100–200 nmol/l. According to animal experiments and human cases D-vitamin

toxicity (e.g., calcification of soft tissues) is associated with constant plasma levels of over 300–500 nmol/l.

The optimum level of 25(OH)-D of 80–100 nmol/l is suggested by the following: **a)** the natural UVB-induced concentration is not exceeded, **b)** the absorption of calcium is optimal while no hypercalcemia is present, **c)** the suppression of the parathyroid hormone is maximal, **d)** the hydroxylation of D₃ by the liver is not saturated, i.e., no accumulation of the D₃ in the fat and muscular tissue occurs, and, **e)** clinical evidence shows beneficial effects on bone density and prevention of fractures.

The experts in the US and Canada have recently recommended a daily supplementation of 1 000–2 000 IU of vitamin D₃ instead of the traditional 400 IU usually present in a spoonful of cod liver oil. Due to confounding factors (sun exposure, diet and age) only time will show the impact of such a recommendation on the average vitamin level in the population.

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Crushing of depot tablets may cause overdoses

During autumn 2008 the National Agency for Medicines received an adverse drug reaction report related to oxycodone sustained release tablets: **A female patient, around 60 years old, suffered from metastasised lung cancer, and was receiving oxycodone depot tablets for the treatment of pain. One morning she was having swallowing difficulties, and the oxycodone depot tablets were given to her crushed. During the same morning she developed shortness of breath. She received oxycodone oral solution as further pain medication, and in the afternoon a phentanyl patch was attached to her skin. She expired within two hours from that.**

Oxycodone is an opioid agonist, and the most significant risk related to its use is respiratory depression. Depot tablets release the active ingredient slower than short-acting oxycodone preparations, and the SPC for oxycodone depot tablets

marketed in Finland include the following or similar warning: *Depot tablets must be swallowed as a whole. They may not be broken, chewed or crushed. Breaking, chewing or crushing of the tablet may lead to a rapid release of oxycodone which may then be absorbed in the system in life-threatening amounts.* Phentanyl is also an opioid analgesic, and respiratory depression is also a risk related to its use. In depot tablet/capsule the effect of an individual dose has been prolonged by regulating the release of the medicinal substance from the tablet/capsule. This release can be regulated by several mechanisms, but mainly the tablet/ capsule should remain as a whole in order to this regulating system to function.

Swallowing difficulties due to various reasons are prevalent among elderly patients. Also crushing of tablets or opening of capsules is common, and

according to one estimate it occurs at least once a week in over 80% of nursing homes. Crushing of tablets is associated with risks related to hygiene and spillage, and even allergic reactions are a risk through contamination of medicines. Especially one must keep in mind that crushing of depot tablets and other modified release formulations may cause rapid release of the medicinal substance and adverse reactions and overdose symptoms.

If the patient has swallowing difficulties, one should check from the SPCs of his/her medications if a regular or a depot tablet is in question. Primarily a more suitable preparation should be sought (e.g., liquid form) that may be crushed), in collaboration with the prescribing physician. Also the marketing authorisation holder or pharmacy may be contacted for further information.
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Recurrent anaphylaxis associated with respiratory infection

Our patient

A 50-year-old healthy male patient attended the dermatology outpatient clinic at the University Hospital of Turku; he had been referred by a health centre general practitioner for a review due to an anaphylactic reaction which had recurred on two occasions. The patient was not receiving any regular medication. He occasionally used aspirin or ibuprofen for aches or symptoms of influenza. He was not aware of being allergic to anything, but said that he suffered large swellings from midge bites. At school age he had suffered from a rash over the carpometacarpal joint which was thought to be atopic. It was treated with corticosteroid ointments, and no further rash occurred in adulthood. Thyrotoxicosis, which he had developed in his twenties, had been treated with surgery and a somewhat short course of medication until he was symptom-free.

At Christmas 2000 the patient had a respiratory infection which was treated with cephalexin therapy prescribed by a doctor, in addition to which the patient also used aspirin and throat lozenges bought over-the-counter (OTC) from the chemist's. After a two-day course of antibiotics the patient within less than an hour of taking his medicine developed severe dyspnoea together with oedema of the tongue, pharynx and face. He managed to get to an emergency treatment unit, and the condition was relieved with adrenaline. After this episode special restrictions of medication were not considered necessary, and cephalexin therapy was later used without problems.

In spring 2007, in association with respiratory infection, facial and pharyngeal oedema recurred, together with generalised urticaria. Before the flare-up of this reaction the patient had treated himself symptomatically with ibuprofen and throat lozenges. The doctor who had given the emergency treatment referred the patient for allergy assessment later.

Skin prick tests were carried out to reveal the ethiology of the anaphylactic reaction (confirm the diagnosis of anaphylaxis). On arrival for the test the patient brought with him an over-the-counter throat lozenge, which was crushed, and a prick test carried out using this resulted in a reaction (8 mm) which was greater than that caused by histamine (5 mm), as also was that using chlorhexidine (0,5% in water) (9 mm). The throat lozenge also contained benzocaine, which did not cause skin test reactions. The patient had taken this particular throat lozenge twice previously, once in 2000 and on another occasion in 2007. The medical ointments used for hand rash in childhood, which probably contained chlorhexidine, had not as far as the patient could remember caused any skin reaction. But some of the ointments containing a corticosteroid and chlorhexidine used for a leg rash in recent years in fact caused further reddening of the skin instead of curing it.

Conclusions

Chlorhexidine causes contact more commonly than immediate allergy. It is known that IgE-mediated

allergy to chlorhexidine may even cause severe general reactions when chlorhexidine-containing antiseptic preparations are used, for example in association with surgical measures (1). However, patients with a weak skin test reaction often only react to topical use with mild redness in the skin (2). As an antimicrobial substance, chlorhexidine may be contained in cosmetics and medical ointments, surgical soaps, tooth pastes, mouth washes, and hand and wound cleaning agents. The fact that chlorhexidine could be found in oral preparations which are absorbed in the body, came as a surprise even to the doctor. According to a report of the National Agency for Medicines, besides the throat lozenges used by our patient, chlorhexidine is not found in other corresponding over-the-counter products available on the market in Finland. In addition to the topical ointments commonly used and also available as OTC products, small amounts of chlorhexidine are found in a few varieties of nose sprays, vaginal ointments, oral gels and solutions and stomach acid neutralising products.

On examining patients who have developed sudden urticaria, angioedema or a complicated reaction of the anaphylactic type, a careful assessment of the products previously used by the patient, including their composition, is recommended. An allergen which is well-known and judged as quite common may sometimes unexpectedly be found in a product.

Literature see page 23