TABU

1|2009

Lääketietoa Lääkelaitokselta

Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

På svenska | Översättning Mats Forsskåhl

Läs TABU också vid Läkemedelsverkets web-sidor
http://www.nam.fi/publikationer/tabu

In English | Translation Mervi Moisander

Read TABU also on the web
http://www.nam.fi/publications/tabu

Hannes Wahlroos
Professor, Director General (until 12.2.2009)
National Agency for Medicines

Editorial

Many thanks to you all – farewell until we meet again

This is my last Editorial for the TABU journal, so please allow me to reminisce a little.

The inception of the journal can be dated back to spring 1991. The Medicines Department of the Board of Social Affairs and Health, which was established on the vestiges of the National Board of Health, wanted to launch a journal targeted at customers and stakeholder groups, with an emphasis on medicines regulation and other issues related to the pharmaceutical industry. The first publication of TABU's leaflet, Tiedote 1/1992, consisted of eight folded photocopied pages. The Editor responsible for the leaflet was Pekka Eränkö, an experienced writer. TABU, in its present format as a journal, was launched at the beginning of 1993 and I became the Editor at that point.

The leaflet, Tiedote 1/1992, contained a paper by me on its first page, discussing the aims of the publication, TABU. I would particularly like to quote the following paragraph:

> *"Pharmaceutical administration is being reorganised once again. A working group of the Ministry of Social Affairs and Health will make a proposal by the end of January 1992 for the establishment of a pharmaceutical agency under the leadership of the Ministry. Essentially, this would lead to the amalgamation of the Board of Social Affairs and Health and the Medicines Laboratory. Irrespective of the rearrangement of the pharmaceutical administration as a single organisation, the medicines regulatory authorities will without doubt need TABU or an equivalent channel of information of their own."*

This was very much to the point, and is what eventually happened. Hopefully, pharmaceutical administration will have its own voice in future, too. At its best, as several reader surveys through the years have shown, TABU's relevance to its readership is evident. A good publication and good communication also reinforce the identity and profile of the organisation.

Apart from that obtained through reader surveys, feedback about TABU has been very limited. I can, nevertheless, think of two examples: Soon after the launch, one reader, a medical doctor, repeatedly requested his name to be removed from the distribution list because TABU, as the name of a journal, in his mind, was insulting, anathema and degrading. He did receive a few more issues before the dispatches were successfully cancelled. Another example was a reader, a pharmacist, who sent me a postcard depicting beautiful flowers accompanied with encouraging text to congratulate me on my editorial article. It lifted my spirits for many days from then on.

Even the name of the journal has generated responses. A glance at the top shelves of magazine displays in shops reveals that another journal called TABU is published in Finland, but in the field of adult entertainment. Despite the risk of confusion, NAM has steadfastly held on to the name of its journal. Between the editors, there were never disputes about the right to use the name.

The pharmaceutical sector relies on TABU and the papers published in it have a faithful readership. For this I am grateful to the many colleagues I have at NAM. I also extend my gratitude to the external collaborators and authors who, from their viewpoint of practical pharmaceutical care and the pharmaceutical sector, have ensured the trustworthiness of the papers. The greatest recognition for the production of the journal is nevertheless due to Inari Stenberg, Pirkko Paakkari, Erkki Palva and Marja Forsell, who have formed the core editorial team throughout the years and worked to bring TABU to the fore to become an important pharmaceutical publication in Finland.

On the threshold of changes, I would like to wish all readers of TABU plenty of good reading in the future – in one way or another. Thank you all for your cooperation!

Heikki Valleala
M.D., Ph.D.
Specialist in Internal Medicine
Helsinki University Central Hospital

Yrjö Konttinen
M.D., Ph.D.
Professor of Internal Medicine
Helsinki University Central Hospital

Glucocorticoid–induced osteoporosis (GOP)

Glucocorticoid therapy is the most important cause of secondary osteoporosis and a common indication for medical prophylaxis against osteoporosis.

According to an extensive study carried out in the UK, a long-term, low-dose cortisone therapy (prednisone 2.5–7.5 mg/day) is associated with a 2.6-fold (95 % CI 2.2–3.3) increased risk of vertebral fracture. With a daily dose of prednisone higher than 7.5 mg the risk of vertebral fracture was increased 5.2-fold (95 % CI 4.3–6.3) in patients in whom the most common therapeutic indication for glucocorticoids was respiratory disease (1). The risk of fractures increased significantly as early as within three months of the introduction of the cortisone therapy. However, in little more than a year after discontinuing the therapy the risk of fractures decreased to the level of that of the control subjects.

In another study, extravertebral fractures were found to increase by 54% during the first year of therapy with a dose of prednisone of over 7.5 mg per day. The risk of fractures correlated more closely with (each) daily dose than with the cumulative total dose (2). In patients on glucocorticoid treatment, bone fractures occur at higher bone density values in comparison with those who do not receive this treatment (2). The explanation is thought to be the reduced bone quality due to the effect of glucocorticoid therapy.

The pathogenesis of GOP

Following the introduction of glucocorticoid therapy the bone mineral density is rapidly reduced due to increased bone resorption. As the glucocorticoid therapy is continued, the rate of bone loss slows down and is mainly due to reduced bone formation. Glucocorticoid therapy mainly effects the rapidly forming cancellous bone rather than the more slowly renewable cortical bone. Indirect effects include reduced absorption of calcium from the intestinal tract and reduced reabsorption in the kidneys. Glucocorticoids also reduce the secretion of gonadotro-pins and the growth hormone, which results in increased bone catabolism and reduced regeneration. The catabolic effect of glucocorticoid therapy on the musculature also causes myasthenia, which can increase the risk of falls (3).

The direct effect of glucocorticoids on the bone cells is an important factor in the pathogenesis of GOP. According to data obtained from animal studies, glucocorticoids increase the effect of bone-catabolising osteoclasts by prolonging the lifetime of these cells (4). This explains the rapid reduction in bone density after the introduction of glucocorticoid therapy. Nevertheless, glucocorticoids increase the programmed cell death rate of osteoblasts and osteocytes thereby reducing their activity (5). Oseoblasts are cells on the outer surface of bone which form new bone; their activity is reduced by glucocorticoids. Bone-forming osteoblasts are imbedded in the bone and develop into osteocytes, located in lacunae in the mineralised bone matrix, forming a three-dimensional cell network amongst themselves, as well as linking with other bone cells. Osteocytes play an important role as sensors of mechanical loading of the bone and promote the repair of micro-damages accumulated in the bone. If osteocytic function is inhibited, the result may be an accumulation of irreversible microdamages, which reduces the bone's biomechanical quality. Glucocorticoids therefore also increase the risk of fractures by mechanisms which are independent of changes in the bone density (5, 6).

In the prevention and treatment of GOP, an important consideration is that bisphosphonates, as well as oestrogens and calcitonin, protect osteocytes against cell death caused by glucocorticoids (6). This effect has been found in bisphosphonates even at rather low concentrations, and the various bisphosphonates are equally effective in this respect. The antiresorptive efficacy varies greatly between

the different bisphosphonates, with the most recent aminobisphosphonates being over a thousand times more potent in comparison with the first generation bisphosphonate, etidronate (7).

The medical treatment of GOP

It should be ensured that everyone on steroid therapy has an adequate daily intake of calcium and vitamin D. Bisphosphonate or other effective anti-osteoporosis medication is often also needed to prevent glucocorticoid-induced osteoporosis (8, 9). Wallach et al. (10) reported that a daily dose of 5 mg risedronate had, within one year, reduced the relative risk of new vertebral fractures by 70% in comparison with a placebo. The average lumbar vertebral T-score at the start of the study was -1.2 and the average dose of prednisone used throughout the study was 12 mg per day. At the end of the study the difference between the groups regarding the change in bone density in the lumbar vertebrae was less than 3 %. The rather small difference in the bone densities between the groups cannot explain the significant decrease in the number of vertebral fractures in the active treatment group. The decrease in the risk of fractures was based, in all probability, on the ability of bisphosphonates to inhibit the negative effect that glucocorticoid therapy has on bone qualitative properties.

In a recent study, 18 months treatment with teriparatide increased the lumbar vertebral bone density significantly more than a daily dose of alendronate (7.2% vs. 3.4%). More importantly, a significantly smaller number of new vertebral fractures were detected in the teriparatide group (0.6% vs. 6%) (11). The result supports the perception that teriparatide is escpecially appropriate in the treatment of severe axial osteoporosis.

Future perspectives

In addition to the parathormone analogue teriparatide, other bone therapies with an anabolic effect may also be beneficial in the treatment and prevention of GOP. The effect of glucocorticoids on osteoblasts is mediated partly via the inhibition of the important Wnt signalling path in the osteoblastogenesis. By inhibiting Wnt antagonists, the effect of glucocorticoids on the osteoblasts could be reversed; one example is the monoclonal antibody against sclerostin (AMG 785) (3, 12). For example, strontium ranelate, one of the current anti-osteoporosis drugs, increases bone formation and inhibits its catabolism and would, in theory, be very appropriate in the treatment of GOP.

Another approach is the attempt to develop new glucocorticoids with anti-inflammatory effect but less effect on bone. These types of drugs include nitrosteroids, the effect of which is enhanced by their slow release of NO; glucocorticoids which accumulate in inflamed tissues and are incorporated into liposomes; and, in particular, the selective glucocorticoid receptor agonists (SEGRA), which have a dissociative effect, i.e. anti-inflammatory effect via transrepression, but no adverse effects transmitted via transactivation (13). Budesonide exerts an anti-inflammatory effect in the bowel, but, due to the effective first-pass metabolism, concentrations in the systemic circulation remain low.

Treatment recommendations for GOP

An adequate daily intake of calcium (a minimum of 1 000 mg) and vitamin D (800 IU) is recommended for everybody on steroid therapy (14). Bisphosphonates are the drug group of choice for the prevention and treatment of GOP. The American College of Rheumatology (ACR) recommends bisphosphonates for patients who are prescribed prednisone therapy (5 mg/day or higher) for a period of three months at least. Those who have used prednisone (5 mg/day) for longer, are advised to commence bisphosphonate therapy with osteopenic bone density values (T-score $\leq$ -1) (15). According to a Dutch recommendation (Figure, see p. 5), bisphosphonate should be prescribed when prednisone is started at a dose $\geq$ 15 mg/day. When the daily dose of prednisone is 7.5–15 mg/day, the introduction of bisphosphonate therapy is recommended in postmenopausal women and in men over 70 years old. A decision to start anti-osteoporosis therapy in patients younger than this is based on the result of bone density measurement and general risk factor assessment (16). It is recommended that the risk assessment should cover all the factors which increase the risk of fracture, independent of bone density. There is a new international fracture assessment tool (FRAX) to use for this assessment (17;www.shef.ac.uk/FRAX/) and a similar Finnish osteoporosis index (18, 19). In the prevention of fractures it is also important to identify and eliminate other risk factors for falls (by optimising CVS and CNS medication, improving vision and lighting, improving safety in the home and environment, using walking aids, making the correct choice of shoes, and using anti-slip devices) (20). Hip protectors used by nursing home patients have been proven to decrease hip fractures, but their use is associated with various problems such as compliance (21, 22).

Literature

See page 6.

Johanna Linnolahti
Senior Pharmaceutical Inspector
National Agency for Medicines (NAM)

Summary

A review of the activities of pharmaceutical wholesalers

According to Section 77 of the Medicines Act (395/1987), it is the responsibility of the National Agency for Medicines to inspect pharmaceutical establishments as often as required by the appropriate pharmaceutical regulation. In practice, in addition to the inspections, regulation is carried out by means of standardized guidance, general advice given to entrepreneurs and by various reviews.

NAM's Administrative Regulation regarding good distribution practices for pharmaceutical wholesalers was revised during 2007, and the new Regulation 4/2007 came into force on 1.1.2008. In January 2008 NAM sent 92 drug wholesalers a request for a review of the company's pharmaceutical wholesale activities. In the review questionnaire the licensees were asked for details about their accountable director, about their drug distribution and its scale, storage of drugs, product defects, customer complaints, and about obligatory storage arrangements. Besides the reviews, companies were also asked to submit to NAM copies of standard operating procedures relating to returned products and customer complaints, and regarding procedures on shelf life and transport temperatures.

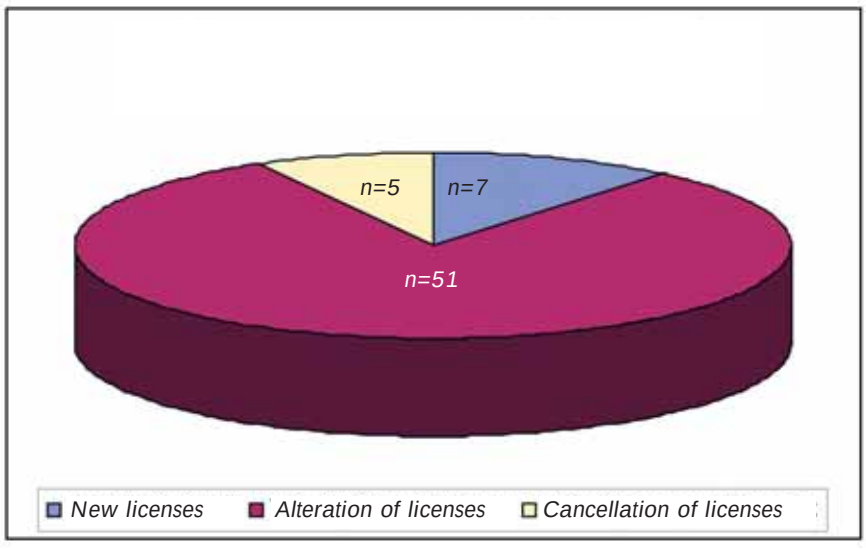

Figure. Total number of decisions concerning licenses of pharmaceutical wholesalers in 2008.

The replies received showed that some of the licensees had neither started their licensed activity at all, or the business had been suspended for longer than the license allowed. Consequently, in addition to the cancellation of some licenses, the review also resulted in a great number of renewals of wholesale licences. In 2008, NAM processed a total of 63 applications from pharmaceutical wholesalers. The number of applications from pharmaceutical wholesalers increased by about 62% in total in comparison with 2007 (n=39), (fig.).

The review questionnaire served its purpose well in reflecting the present situation relating to pharmaceutical wholesalers at an opportune moment, with the new Administrative Regulation regarding their licensed activity coming into force. The review will facilitate improved, more precise targeting of enforcement activities on pharmaceutical wholesalers, keeping in mind future challenges. The review clearly also improved the maintenance of pharmaceutical wholesalers' own quality system.