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TABU

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Editorial

Summary

Hannes Wahlroos
Director General
National Agency for Medicines

Editorial

Norms to their rightful status

Regulatory control, i.e. the imposition of norms by competent authorities in order to control business and industry, has again become the subject of public debate. Contrary to the health care sector in general, the pharmaceutical sector is known to be under strict normative control. It is similarly subject to heavy legislative and normative controls internationally.

Times do change, however, and the need arises to review the regulations and directives issued by authorities, with regard to the contents, as well as the powers to impose such control measures. Such reviews are usually carried out *ex officio*, but external pressure groups may also make themselves heard occasionally.

Following a complaint about the powers of the National Agency for Medicines, Paavo Nikula, the Council of State's Chancellor of Justice, decided on 13 February 2001 to ask the Ministry of Social Affairs and Health to speed up its review of the nature and extent of powers delegated under the Medicines Act, with reference to the new constitution. National Agency for Medicines' (NAM) regulation 3/1999 was at issue. It contained a prohibition on the advertising of pharmaceuticals to the public by pharmacies outside their regular premises. Although NAM could not be said to have exceeded its powers when issuing the regulation, the matter was subject to several interpretations, and the regulation should be placed in abeyance pending an investigation. That is what the National Agency for Medicines has done.

The Ministry of Social Affairs and Health has promptly begun to investigate the matter, and a new appraisal of the correct status of normative control in legislation, government decrees and regulations issued by public authorities is pending.

Especially the fundamental regulations controlling the promoting of pharmaceuticals and the regulations currently of normative control status, should be included in the Medicines Act. Let us look at two cases, in which the need to upgrade control practices is obvious, as the present regulative status is insufficient.

The first case concerns the prohibition on advertising prescription medicines to the public. This prohibition is common in Europe, and particularly in the European Union it is quite unambiguous. In Finland, the National Agency for Medicines has promulgated a matching regulation. Despite that, most pedestrians in Finland can see certain prescription medicines being covertly advertised in the street in posters advising consumers to ask their physicians to prescribe the product in question. This result of innovative thinking by the pharmaceutical industry is clearly a contravention of the spirit of the marketing prohibition. Stricter legislation is clearly needed.

The other case concerns the advertising of medicines by pharmacies outside their premises. When issuing regulation 3/1999, the key argument of the National Agency for Medicines was that Finnish pharmacies should retain their role of independent experts towards the consumers. The consumer must be able to believe that his medication needs are not dictated by the pharmacy's advertising campaign. A system whereby pharmaceutical retailers are acting as marketing partners of the pharmaceutical industry does not fit in with the present objectives of our health care policy. Seeing that pharmacies appear to have conflicting views on the basic nature of their business, regulations must obviously be spelt out more clearly. In his resolution, the Chancellor of Justice stated that the objective of NAM's regulation was in agreement with Section 1 of the Medicines Act.

There are dozens of authorisations for normative control in the legislation on pharmaceuticals.

In addition to adjusting the level at which regulations may be issued to match the new constitution, it is possible that other reasons for reviewing the contents of regulations or legislation in some way are discovered. From NAM's viewpoint, it is important that normative control promotes the safety of medicines on the one hand, and the rational and safe usage medicines on the other hand.

Translation Liisa Fellman-Paul

Summary

Matti J. Välimäki
Associate Professor, Chief Physician
Dept of Endocrinology
Helsinki University Central Hospital

Drugs for osteoporosis - when and which one?

The goal of prophylaxis and management of osteoporosis is prevention of bone fractures. The cornerstones of prophylaxis include sufficient intake of calcium and vitamin D, regular exercise and avoidance of smoking. These are also the main emphases in osteoporotic patients. In addition to treating osteoporosis, osteoporosis medication can also be considered for the prophylaxis of osteoporosis in patients whose bone mineral density approaches the severity of osteoporosis at a stage of life when the bone condition is likely to deteriorate (menopause, long-term treatment with corticosteroids).

Vitamin D

Finns have a surprisingly low level of vitamin D. The deficiency of vitamin D in the elderly has been established but adolescents appear to be a new risk group. The vitamin D level is best reflected by the serum vitamin 25(OH)D concentration. When the concentration is decreased, the serum calcium level is reduced, which causes increased parathyroid hormone (PTH) secretion and serum PTH concentration. The parathyroid hormone stimulates bone change, especially in the cortical bone, and this exposes the patient to hip fracture. In population studies the PTH level was elevated when serum 25(OH)D concentration was reduced to a level of 37 nmol/l. This, which is nowadays considered the minimum level of vitamin D concentration, is distinctly higher than the minimum level of Finnish reference values of 20 nmol/l. In October 1998, vitamin 25(OH)D concentrations below the minimum level were found in two out of three patients (average age of 63 years) in Finnish hospital internal medicine wards and in two out of five patients (average age of 44 years) in out-patient wards. In winter 1997, a similar deficiency in vitamin D was found in two out of three girls in south-western Finland and, according to our own yet unpublished findings, in two out of three Finnish conscripts at the beginning of summer 2000.

Several studies have shown that co-administration of calcium and vitamin D can prevent hip fractures and other fractures. Co-administration of calcium and vitamin D is important. No benefit was found in the use of vitamin D alone. The daily intake of calcium should total 1–1.5 grams and vitamin D 400–800 Units. Irrespective of age, Finns should consider a daily vitamin D supplement of 400 Units during winter time. The elderly, whose outdoor pursuits are infrequent, can safely be given daily doses of 800 Units all the year round; intoxication has only developed with doses amounting to 10,000 Units or more.

It should be recognised that placebo groups in osteoporosis drug studies have as a rule also received calcium and vitamin D. If a specific osteoporosis medication has decreased bone fractures more than the placebo, the benefit has in that case been additional to that from the co-administration of calcium and vitamin D.

When should an actual osteoporosis drug be introduced?

Indications for pharmacological treatment of osteoporosis include past history of osteoporotic fracture or bone mineral density equal to that of the osteoporotic stage in the lumbar vertebrae or femoral neck *[bone mineral density 2.5 standard deviations (= about 25%), or more, below the average bone mineral density in young adults = so-called T-score below ≤ – 2.5]*. The decision of whether to resort to treatment is influenced by the age, overall situation, other illnesses and medical treatment of the patient.

Poor availability of density measurements is a problem in the diagnosis of osteoporosis. Health centres should afford their doctors the opportunity to refer their patients for density measurement which can be either bought from a hospital or from the private sector. The unit carrying out the measurement will then provide an account of the examination which the patient takes to his or her own doctor. The examination can be bought directly from a hospital without an unnecessary and costly appointment at an outpatient department. Strict criteria could be applied to referrals for treatment. The first patients to undergo examinations should be women over 65 years of age with a history of fractures (= confirmation of diagnosis of osteoporosis) and who do not use estrogen treatment or other drugs protective against osteoporosis. The first diagnostic examination is the most important and follow-up examinations are not absolutely necessary.

Which drug?

Osteoporosis should be treated with drugs which have been shown to prevent bone fractures in controlled

clinical studies (table). On-going placebo-controlled studies have indicated that vertebral fractures are preventable by several drugs, but hip fractures only by alendronate and risedronate in addition to calcium and vitamin D. Proof of prevention of hip fractures in estrogen therapy is based only on control and cohort studies. The choice is governed by the price and efficacy of the drug, site of the osteoporosis (treatment of osteoporosis of the upper femur only with drugs which have prevented hip fractures) and any other benefits and adverse effects of the drug which are considered in the total assessment of the patient's situation. Estrogen treatment is justified by symptoms of menopause. A history of breast cancer in the patient, in the family or as a phantom in the mind may deter estrogen treatment and justify the use of bisphosphonates (alendronate, etidronate, risedronate) or raloxifene of the selective estrogen receptor modulator (SERM) group which in a 5-year follow-up has prevented the occurrence of breast cancer. Mild hypercholesterolaemia justifies estrogen treatment and the use of raloxifene, both of which reduce serum total cholesterol and LDL cholesterol by 10–15%. Problems associated with menstruation constitute a contraindication for estrogen treatment and support the use of biphosphonates, or raloxifene which has no effect on the endometrium, causes no menstrual bleeding and does not require progestine supplements. The analgesic properties of calcitonin are useful in the context of vertebral crush fractures.

Even though placebo-controlled studies do not indicate that biphosphonates cause gastro-intestinal irritability, these drugs are nevertheless often associated with various alimentary tract symptoms. Patients with a history of abdominal disorders are usually excluded from clinical studies, which may explain differences in result in practical experience. Raloxifene will not prevent hot flushes and its use may be associated with cramps.

In association with painful vertebral fractures calcitonin can readily be combined with another osteoporosis drug. According to two studies, the combination of estrogen and alendronate or etidronate is more effective than either of the drugs alone, and the effect of alendronate alone is likely to be superior to that of estrogen.

Drugs which reduced fractures in controlled trials

In the vertebrae

Estrogens
Raloxifene
Alendronate
Etidronate
Risedronate
Calcitonin (200 Units/day)

In the hip

Alendronate
Risedronate
Calcium + vitamin D

Osteoporosis in men

Diagnosis of osteoporosis in men should be followed by measurement of serum testosterone. If the level of testosterone is reduced, replacement therapy should be started. It should be borne in mind that men on long-term corticosteroid therapy may need testosterone replacement therapy because corticosteroids reduce the concentration of testosterone. Idiopathic osteoporosis in men is treated with calcitonin and biphosphonates. Among the above mentioned drugs only alendronate entitles men to full refund in the Finnish health insurance scheme. Even though only alendronate has been proved to reduce fractures in osteoporotic men so far, etidronate and risedronate should also entitle men to full refund of medical costs. Their effect when compared with alendronate has been very similar to that in studies carried out on women, and it is hard to imagine why the response of the male skeletal system should vary from one biphosphonate to another. Alternatives in the treatment of osteoporotic men are also needed in case, for instance, alendronate should for some reason prove inappropriate.

Secondary prevention should be the starting point

Cholesterol-lowering medication is the most cost-effective treatment in secondary prevention, i.e. those with coronary artery disease would receive the greatest benefit from it. The same is most likely to apply also in the treatment of osteoporosis. The biggest benefit would be received by those with a history of fractures, and they should be the first ones to be covered by the treatment. The first fracture is predictive of another occurring. After the first vertebral fracture, the risk of another vertebral fracture will be five-fold and that of a hip fracture will be double. After a second vertebral fracture, the risk of a later vertebral fracture is 11-fold. After a wrist fracture, the risk of a hip fracture is double and after a hip fracture the risk of any fracture is 2–5-fold. Fractures can be prevented with new drugs in those with a history of fractures. Placebo-controlled studies of patients who have sustained a vertebral fracture showed that the occurrence of a new vertebral fracture was reduced by 47% with alendronate, 41% with risedronate, 30–50% with raloxifene and 36% with intranasal calcitonin when the daily dose totalled 200 Units. The NNT figures *(number needed to treat*) in these studies show how many patients had to be treated during the study in order to prevent one patient from sustaining a fracture. In those with a history of fractures, the figures have been realistic and varied between 9 and 22 in 3-year studies. If the criterion for inclusion in the study has only been a mineral density level similar to that in osteoporosis without a fracture, the increase in figures has been manyfold and varied between 35 and 58. The difference is explained by the difference in the incidence in various placebo groups. New fractures in the placebo group among those with a history of fractures occurred in 15–26% of patients during three years, whereas the percentage was 5–6% in patients with osteoporosis diagnosed on the basis of the density criterion.

How can the cost-effectiveness of treatments be improved?

In addition to those who have already sustained a fracture, the diagnosis and treatment of osteoporosis should be focused on people in the appropriate age group. Osteoporosis with consequent occurrence of fractures increases sharply with age. Age is an independent predictor (= independent of bone mineral density) of a fracture in that its risk becomes 2–3 times higher with every ten years of age. The efficacy of medical treatment is proven in the elderly; all the above studies have been carried out in people with an average age of 70. Furthermore, the cost-effectiveness of treatment is definitely better in the elderly who, independently of their bone condition, sustain fractures more frequently than the young, in whom fractures in fact seldom occur.

The question still remains, however, which is the most cost-effective age to start the treatment of osteoporosis. In studies where alendronate and risedronate have diminished the occurrence of hip fractures by 40-56%, the average age of subjects varied between 68 and 74 years. Due to the low incidence in the placebo group (only 2–3%) the NNT figures in these studies are unreasonably high (81–93). Consequently, it would seem that medical treatment to prevent hip fractures should be directed towards even older people who sustain these fractures frequently. Sub-group analyses in the risedronate study on the prevention of hip fractures arrived at as good an NNT figure as 40 during a 3-year course of treatment, when patients of the average age of 74 years in addition to a low mineral density at the femoral neck (T-score < – 3), also had at least one vertebral fracture. Consequently, to improve the cost-effectiveness, sufficiently old patients should be treated whose bone mineral density is at a level similar to that of osteoporosis and who have previously had a fracture. The cost-effectiveness is naturally improved by any other beneficial extra-skeletal effects of the drug (prevention of breast cancer, beneficial effect on risk factors of cardiovascular diseases).

Treatment of the skeletal system is not sufficient

The development of vertebral fractures is to a great extent dependent on internal risk factors, i.e. poor bone condition. The vertebra can be fractured in normal everyday routines without any external trauma. A hip fracture is a different story. Internal risk factors are decisive in the fracture, the development of which nevertheless usually always requires significant external trauma. There is a 13-fold increase in the risk of hip fractures between the age of 60 and 80. Conditions which can be treated with medication (decrease in mineral density, accelerated absorption of bone) explain a 4-fold increase. The increase in accidental falls is responsible for the rest, the 9-fold increase. Consequently, the ultimate emphasis should be on the prevention of accidental falls and protection against them. Protection may be easier than prevention. A significant Finnish study showed that the risk of hip fractures was decreased by 60% in people using hip pads during a 2-year follow-up. In order to prevent one hip fracture, 41 people had to wear pads for a year. If the NNT figure was calculated on five years, eight people would have had to wear pads for that period of time to prevent one hip fracture. The problem at least up until now has been treatment compliance. About a third of the patients refused to wear any kind of pads and 9 of the 13 fractures in the pad group occurred while the pads were in the wardrobe.

What is to be expected in the future?

A 70 mg tablet of alendronate will also be introduced on the Finnish markets in September. It is administered only once weekly, in a way similar to that of the present 10 mg tablet which is administered once daily. Once-weekly administrations proved to be equally as effective as once-daily administrations assessed according to markers of bone mineral density and bone change. At least some patients show improved compliance with treatment when the administration which is felt to be awkward has to be carried out on only one day a week.

For a long time a preparation which would improve bone formation has been anticipated. Somewhat surprisingly, perhaps, subcutaneous parathyroid hormone injected once daily has proved to be such a preparation. PTH with only a couple of hours of effect is benefical to the bone whereas an ongoing increased concentration of PTH is harmful. A very recent publication showed that a 1.5-year course of treatment in postmenopausal women, who had sustained at least one osteoporotic vertebral fracture, increased the mineral density of lumbar vertebrae by 9-13% and decreased the risk of a new vertebral fracture by 65–69%. An answer is being sought at present to the question of how this treatment could be naturally combined with modern drugs preventing bone loss. Administration of parathyroid hormone for 1–2 years which is then followed up by treatment preventing bone loss would seem the solution.

Conclusion

Several effective drugs exist today for the treatment of osteoporosis and prevention of osteoporotic fractures. Patients with an existing history of fractures should be the first to be included in the management scheme. Urgent agreement needs to be reached on deciding who will give advice on treatment to these patients – the surgeon involved in the treatment of the fracture, or the GP?

Summary

Ali Bardy
Senior Medical Officer
Pharmacological Department
National Agency for Medicines

New administrative regulation on clinical trials

The National Agency for Medicines (NAM) has issued a new administrative regulation, "Clinical trials on medicinal products in human subjects", which came into force on 1 May 2001.

The Act and the Decree on medical research were promulgated in Finland in 1999. This is the first time in Finland that the establishment, duties and ethical principles of Ethical Committees have been covered by legislation: this also includes issues like the consent of the subject and the underaged and handicapped as subjects.

The EU guidelines on good clinical practice, GCP, were issued in 1997. They include, for instance, a vocabulary, advice on the content of a research plan and patient information leaflet, and documents necessary for the trials and the safe-keeping of these. The guidelines can be found on the Internet pages of the EMEA **www.emea.eu.in/pdfs/human/ich/013595en.pdf.**

Some of the sections which differ from those in the previous regulation are presented below.

Ethical assessment

Up till now a statement by the Ethics Committee has been required to be enclosed with the notification to the NAM of a planned trial, whereas from now on it is sufficient to submit the statement to the Agency before starting the trial. The notification of a planned trial can now be submitted simultaneously to both the Ethics Committee and NAM. The NAM has 60 days following submission of the notification to request any additional reports necessary. If there are no requests for further reports within the prescribed time limit, the trial may start as soon as the supporting statement of the Ethics Committee is submitted to the NAM. The researcher should nevertheless be prepared to receive requests for further reports and suggestions of changes in the research plan and consent document from both the Ethics Committee and the Agency.

Reports of adverse reactions

The legal obligation to notify the NAM of adverse reactions has been narrowed and made easier. Previously, every severe adverse event had to be reported to the NAM. Nowadays it is sufficient to report adverse reactions which are both severe and unexpected. An adverse reaction differs from an adverse event in that an adverse event with a possible causal relationship with the medicinal product is called a reaction. The due dates of reports have been extended. Severe, unexpected adverse reactions which have led to death or to a life-threatening situation must be reported to NAM within seven days. Other severe unexpected adverse reactions must be reported within 15 days. If the adverse reaction is not both severe and unexpected, a reference to it in the report of the trial results is sufficient. The terms 'severe' and 'unexpected' are explained at the start of the regulation, where the rest of the terminology used is also defined. The reports should preferably be made in writing; fax can be used in exceptional cases, but they should not be made via e-mail.

A new feature is an annual summary of suspected severe adverse reactions in the course of long-term trials, including a report on the safety of the subjects of the trial.

Other revisions

Definitions of terms used in the regulation are explained at the beginning. Coherent terminology will hopefully clarify the content of the regulation and facilitate the exchange of information.

The regulation contains an obligation for researchers to report their trial results within one year of completion of the trial. If the trial is interrupted prematurely, the reasons for the interruption and the causes responsible must be reported to the NAM within 15 days. The researcher has an ethical obligation to publish his or her research results. The NAM for its part aims to monitor important information and ensure that it is not kept secret but is made available to the authorities and the entire medical community.

Practical needs are served by detailed instructions regarding exemption from the processing fee, the contact person for multicentre studies, and the start and completion of trials.

Where to obtain the regulation?

The regulation is available via the Internet. The home page of NAM **www.nam.fi** has links to the Finnish and Swedish texts and the unofficial translation in English. The home page also contains links to forms for notifications. Printed English version of regulation can be ordered by phone +358 9 4733 4213 in NAM.

Translation Mervi Moisander