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Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

På svenska | Översättning Mats Forsskåhl

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Editorial

A new Finnish Medicines Agency – what is happening?

On 15.5.2009 the President of the Republic submitted the Finnish Parliament a government bill for a law relating to the new Medicines Agency, Lääkealan turvallisuus- ja kehittämiskeskus: this will be an administrative Act. The Ministry of Social Affairs and Health had previously made a decision to relocate the Agency to Kuopio. I started in my post as the Director General at the National Agency for Medicines in February in the middle of reorganisation. It appears that I started my work in the eye of the storm, as the editorial of TABU described the situation of the pharmaceutical administration last autumn.

The aim of the government bill is to reorganise the administration of pharmaceutical service in such a way that the pharmaceutical expertise in the administrative field of the Ministry of Social Affairs and Health would be concentrated in the new Agency.

The objectives are to improve the role of pharmaceutical expertise in the social and healthcare service system, improve the process of marketing authorisations and pharmaceutical regulation, ensure the availability of medicines nationally, improve the safety of medicinal products and medications and also to contribute to the research and development of the pharmaceutical field. One of the objectives is also to arrange for a national evaluation of the therapeutic and economic value of medicines and to develop influence of the pharmaceutical field internationally and within the EU.

The Ministry of Social Affairs and Health requested statements from the stakeholder groups and held a consultation on the options in April. The majority of the written statements considered a reorganisation of the pharmaceutical service justified. While amalgamating the duties relating to marketing authorisation and regulatory affairs into the same organisation with research and development, emphasis was given to safeguarding the independence of the various tasks and financing.

It is proposed that the main responsibilities of the new Medicines Agency should include responsibilities involved with marketing authorisations and regulatory affairs, pharmaceutical research and development, and the generation and distribution of pharmaceutical expertise in order to improve the impact of pharmaceutical service and therapies.

According to the government bill the new Agency will improve public health and safety by regulating medicinal products and medically used tissues and by developing the pharmaceutical field. Research and development activities will also support decision-making concerning medicinal products in society. The Agency intends, for example, to carry on pharmaco-political and pharmaco-economical research and to improve co-operation within research and development in the pharmaceutical field. In addition to guaranteeing the safety of medicinal products, the Agency will also guarantee the safety of medically used tissues. The reorganisation would, however, mean that responsibilities associated with medical devices would be borne by the National Supervisory Authority for Welfare and Health (Valvira). The new Agency will maintain close co-operation with pharmaceutical entrepreneurs and stakeholder groups.

The government bill will provide a framework for the new organisation and will direct the development of new operators in the pharmaceutical field. In the development of operational models and organisational structures for the new Agency attention will be paid to the impartiality of the responsibilities involved in marketing authorisations and regulatory affairs and the independence of scientific research. It is also important that the working methods are formulated in such a way that the Agency will be able to serve the pharmaceutical field and health care successfully in accordance with the aims of the reorganisation.

The National Agency for Medicines (NAM) in its present form has devoted significant amounts of its expertise to the preparation of this government bill. Top know-how is available at NAM to promote the reorganisation, which requires open-mindedness, courage and expertise, not forgetting solidarity which is also required. Reforms provide a number of opportunities, but they also involve risks. Resources should be allocated to the careful development of this reform, to minimise risks and, above all, to ensure that pharmaceutical regulation is safeguarded in a very challenging and multifaceted situation of change.

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An overview of reports on adverse incidents associated with the use of medical devices

The National Agency for Medicines supervises and promotes the safe use of medical devices. This work includes the processing of reports on adverse incidents and the reviewing of the associated incidents together with the manufacturers and users of the devices. Reporting of adverse incidents is a legal requirement. Such reports are received from users, manufacturers, and other responsible national bodies. NAM compiles the reports received from various sources and forms an overall view of the incidents. Information received is subsequently used for preventing adverse incidents from occurring. Information about incidents detected in one EEA member state will where necessary even be made use of in other member states. Information put together from reports on adverse incidents can be examined not only with regard to safety aspects but also in the light of ensuring a faultless reporting system.

Reporting an adverse incident

The premiss of a report on an adverse incident is constituted by an association with a medical device which causes or could cause serious harm to the patient, personnel or another individual. For the system to operate completely effectively it is required that adverse incidents should be recognised and reported. Users of devices and accessories are keys to the system. Without them, information about incidents would not be passed on. Reports on adverse incidents are submitted to NAM by the users of devices, who should also inform the representatives of the manufacturers of the devices. A device and the associated materials involved in the adverse incident should be maintained unchanged until the manufacturer has had an opportunity to establish and document the incident. In the present European vigilance system, the responsibility for resolving the incident lies with the manufacturer. A report on the adverse incident and on the measures intended and taken is submitted by the manufacturer to the authorities of the country where the incident occurred.

Both users and manufacturers of devices should follow the regulations stipulated for reporting of adverse incidents (Administrative Regulations by NAM 4/2005 and 5/2005). Despite the regulations in force it still appears to be difficult to recognise and submit a report on an adverse incident. To make it easier to recognise adverse incidents NAM sent a circular letter to healthcare units in October 2008 reminding them about their responsibility to report any incidents they detect and giving concrete examples of adverse incidents on which reports should be made. It was also emphasised that the purpose of reporting is to promote the safety of medical devices and that there was no intention of trying to find culprits. Health care units have in recent years introduced voluntary internal reporting systems, which for their part promote the recognition of adverse incidents as well as the reporting of these to the authorities. Reminders, improved motivation, regulations and training are needed in future as well. Both professional users and device manufacturers are still reporting only a proportion of incidents to NAM. Fig. 1 shows the number of reports on incidents submitted by users in relation to reports by device manufacturers relative to adverse incidents that have taken place in Finland. Irrespective of the number of reports submitted annually, the proportion of reports submitted by users is about half of those submitted by device manufacturers. On examining the Figure it should be noted that not even then do all manufacturers report all the ad-

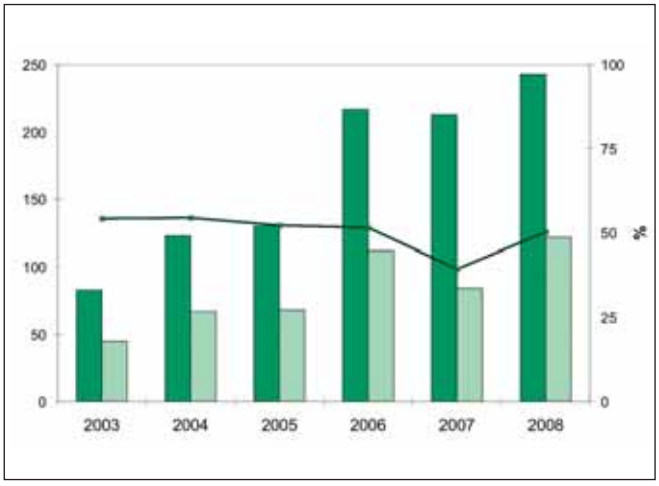

Fig. 1. The number of adverse incidents reported in Finland annually. Reports are made by device manufacturers (the darker column) and by users. The line in the graph depicts the relationship between the two types of reports (percentage scale on the right).

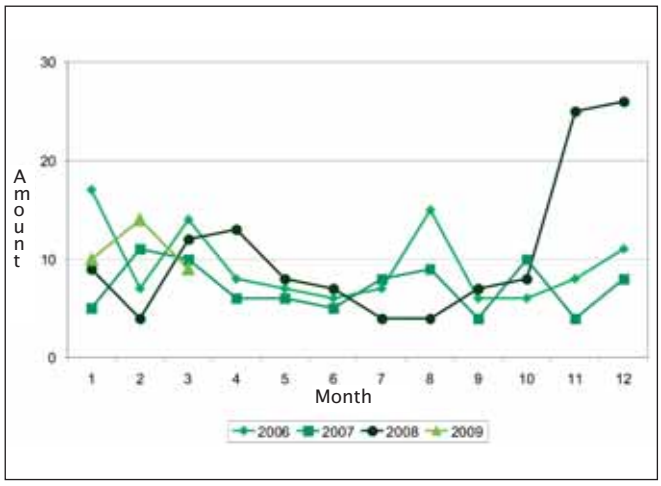

Fig. 2. The number of reports submitted by users monthly during 2006–2009.

verse incidents they detect. Every adverse incident occurring in Finland should be reported by both the user and the manufacturer.

Another graph concerning reporting activity is shown in Fig. 2, in which the number of reports received from users is examined monthly over a period of three years. Following the letter of reminder sent in October 2008, an increase in reporting activity was seen for some months and was in fact three times that in comparison with the previous level.

The number of reports on adverse incidents

The annual total number of reports has increased continuously (Fig. 3). The growth cannot be interpreted as a sign of deteriorating product safety or of an increase in user faults; it is rather a sign of development of information flow, of the reporting system and of the culture of safety. The increase in reports on adverse incidents applies in nearly all reporter groups, i.e. professional users, Finnish and foreign manufacturers and authorities.

Fig. 3 shows those that have submitted reports as users (U), Finnish manufacturers (M), foreign manufacturers (M2), authorities in the European Economic Area (EU CA) and other authorities (Other CA). The graph only shows the proportion of reports concerned with devices in use in Finland. In addition to these reports NAM also receives reports from authorities about products not marketed in Finland. In 2008 the total number of reports concerning adverse incidents processed by NAM amounted to nearly 1 000, about two thirds of

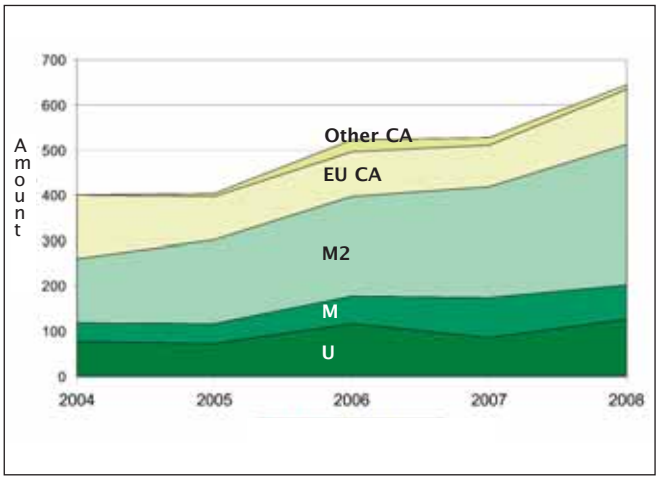

Fig. 3. The development of numbers of reports in the past five years (reports concerning Finland).

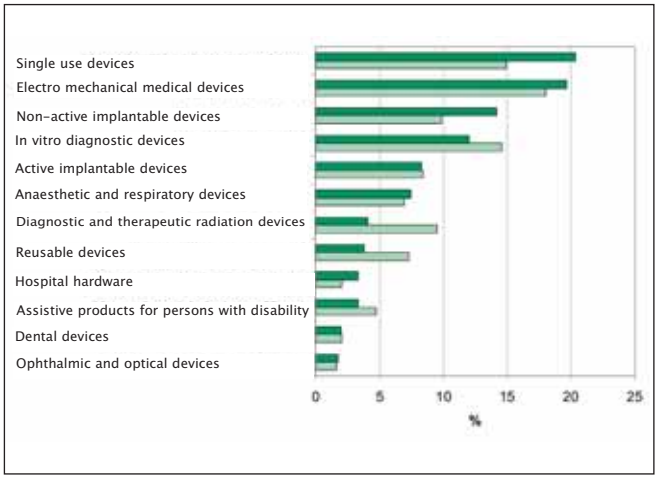

Fig. 4. The relative proportion in percentage of reports on adverse incidents associated with the different groups of devices. The distribution highlighted in a darker colour is the mean percentage in 2000 to 2007 and the one in a lighter colour is the distribution in 2008.

which concerned devices and accessories in use in Finland.

Accurate conclusions cannot be drawn about the number of reports on adverse incidents, partly because several reports may have been submitted on one and the same incident. Initially the report on an adverse incident is typically received from the user or the manufacturer. As reports from both of these sources are relevant for obtaining an overall picture, the missing report is requested where necessary. Reports received from foreign manufacturers are often also followed by a report from the authorities with the aim of informing the other member states.

The number of reports is increased by reports required of the manufacturer concerning any separate remedial measure that the manufacturer needs to take after having examined the incident, e.g. recall of the product from the market.

Product groups associated with adverse incidents

In order to facilitate the processing of common data, standardised grouping of devices has been in use in Europe for quite a long time (EN ISO 15225 – Specification for a nomenclature system for medical devices for the purpose of regulatory data exchange). On examining the reports on adverse incidents according to groups of devices, four groups emerge: products for single use, electrical and mechanical medical devices, sample measuring instruments (i.e. IVD products) and non-active implants (Fig. 4). Considering the number of products on the market, the groups of devices based on the standard are not equally big. Consequently, the group of electrical and mechanical devices, for example, has a wide representation in the reports on adverse incidents. In this group the devices typically representing adverse incidents include patient monitoring equipment and defibrillators. Adverse incidents associated with disposable health care devices have consisted mainly, for example, of mechanical defects developing in the use of catheters. Generally, these incidents are serious when parts of the device remain in the body. Adverse incidents associated with non-active implants have mostly concerned orthopaedic implants, especially endoprostheses. NAM is able to monitor the quality of endoprostheses with the help not only of the reports on adverse incidents but also of the data contained in the implant register.

According to Fig. 4, the division of reports on adverse incident in 2008 into the different groups of devices corresponds relatively well to the long-term medium. The biggest changes can be seen in the reports associated with imaging devices and reusable devices, the relative proportion of which has doubled.

Defibrillators deserve a special mention under the general heading of electrical and mechanical devices. External defibrillators are used both in the resuscitation of patients and in rhythm transfers whereas internal defibrillators are life-maintaining devices since they impose a beat pacing the heart each time they detect a rhythm that needs defibrillation. Defibrillators that fail to function may be fatal to patients. During the past five years regularly about 30 to 34 adverse incidents associated with the use of defibrillators have been reported every year. A little more than half of these concern external defibrillators. A typical adverse incident is created by a functional defect in semi-automatic defibrillators which have come into common use, in which case the device does not detect the rhythm that needs defibrillation. Resuscitation especially in an acute situation under all circumstances requires high reliability from a defibrillator.

Causes of adverse incidents

Fig. 5. shows the distribution of causes of serious adverse incidents relative to Finland in 2008. There is no significant variation in the distribution in comparison with previous years. The majority of adverse incidents are caused by the device becoming defective after introduction into use or being defective already prior to use. The defects can be either mechanical or electrical. The proportion of failures owing to use error is in the range of 10%.

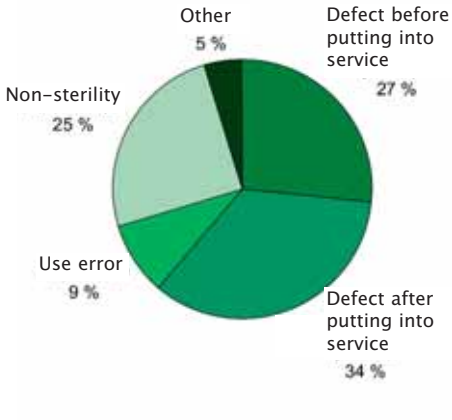

Fig. 5. The distribution of causes of serious adverse incidents that have occurred in Finland in 2008.

Safety information

Medical device safety notice (MDSN) are one method by which NAM aims to prevent the development of new adverse incidents. As a rule, safety reports disclose several reports on adverse incidents associated with the use of one and the same type of device. An average of one to two reports are published annually. The most recent safety report published in the beginning of the year concerns the connections of enteral feeding tubes. All medical device safety reports published are found on the website of NAM in Finnish and Swedish. MDSN reports are also

found on the official websites of authorities of other member states, e.g. the UK Medicines and Healthcare Products Regulatory Agency, MHRA.

Collaboration between authorities

The system of reporting of adverse incidents has become established and works well. As part of their routine, responsible device manufacturers send information about the remedial measures to be taken as a result of detection of an adverse incident to the authorities of all those countries where the device is marketed. Should the manufacturer for any reason not inform other member states about remedial measures, the responsible authority can submit the relevant information to the authorities of other member states. These are called reports of National Competent Authority (NCAR) and are promulgated by means of the use of a common form. In Fig. 3. the proportions of reports from authorities are shown in yellow (EU CA and Other CA).

The number of reports from authorities totalled 308 in 2008. The number of reports submitted by the authorities of the various member states together with the associated references are available on the public website of the European Commission.

New regulations about reports on adverse incidents

The EU Commission has issued regulations about reporting on adverse incidents in its recent Guidelines on a Medical Devices Vigilance System (MEDDEV 2.12/1 Rev 5.5.). These will as and when appropriate replace NAM's earlier guidelines, and in comparison with the earlier procedure the amendments include accounting for misuses and embodying them in the manufacturers' reporting system together with new and stricter time limits for submitting reports. Up until now a report has been required according to the seriousness of the case within either 10 or 30 days, but the new regulation includes a new 48-hour time limit for the incidents that are very serious and which from the public health point of view call for urgent handling.

Adverse incident reporting by entrepreneurs

A new government bill on medical devices and accessories is at present awaiting processing. One of the new issues dealt with in the government bill is the liability of the entrepreneur to report any adverse incidents. An entrepreneur in this sense signifies, for example, an importer, distributor, installer or other handler in the chain in which the device or accessory is transferred from the manufacturer to the end user. In practice this means improved detectability of hazard-causing incidents or device defects and probably also an increase in the number of reports to be processed.

Links associated with the subject

Forms and guidelines for medical device adverse incident reporting to NAM:
http://www.laakelaitos.fi/medical_devices/incident_reporting

The Commission guideline MEDDEV 2.12/1 rev 5: Medical Devices Vigilance System:
http://ec.europa.eu/enterprise/medical_devices/meddev/meddev_en.htm

The authorities' websites and other contact information:
http://ec.europa.eu/enterprise/medical_devices/ca/list_ca.htm

Act on Medical Devices
– a motion to the Ministry of Social Affairs and Health on 29.9.2008:
http://www.laakelaitos.fi/laitteet_ja_tarvikkeet

Conclusion

- The adverse incident reporting system has been successfully harmonised and established in the member states of the European Economic Area. Data relevant to the incidents and statistics involved have been extensively accumulated over several years.

- Processing of individual adverse incidents involving medical devices is always confidential, but utilisation of the filtered information needs to be improved in future in order to prevent adverse incidents. Attempts should be made through feedback and communication to motivate users of medical devices and accessories towards improving the submitting of reports.

- Continuous increase in the total number of reports of adverse incidents under processing presents a challenge. The introduction of electronic forms for reporting accelerate the processing and improve the usage of the system.

As the National Agency for Medicines (NAM) will cease to operate and a new Medicines Agency will be established, it is proposed that responsibilities relating to medical devices be transferred to the National Supervisory Authority for Welfare and Health (Valvira) of the Ministry of Social Affairs and Health.

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Summary

The cardiovascular adverse effects of coxibs – time for interim evaluation

Nonsteroidal antiinflammatory drugs (NSAIDs) were associated with circulatory prothrombotic events in 2004 when the cox-2 selective rofecoxib was withdrawn from the market because of increased risk of cardiovascular events. The cardiovascular problems were explained by the following: 1) the cardiovascular adverse effects of rofecoxib were only an artefacat and due to the aspirin-like protective mechamism of the comparator drug naproxen on the cardiovascular system, 2) the adverse effects of rofecoxib were non-specific and not related to cox-2 -selectivity, 3) the cardiovascular problems were due to the cox-2 selectivity of rofecoxib, and thus is a class effect of all coxibs, and 4) all NSAIDs can cause cardiovascular harm. At the moment, there is evidence to support any of these hypotheses. To find the truth, one has to go through controlled randomized studies including at least 145 000 patients and observational studies consisting of 3,5 million patients. Conclusions of this article are based on the major controlled studies on coxibs and the latest meta-analyses of the controlled and epidemiological studies, as well as some basic research findings on NSAID pharmacology.

Conclusions

- Both traditional and cox-2 selective NSAIDs slightly increase the risk of cardiovascular events.
- The most clear-cut evidence is that involving rofecoxib.
- The cardiovascular risk for both rofecoxib and celecoxib, and probably all NSAIDs, is dose-dependent.
- The risk of high-dose celecoxib is similar to that of traditional NSAIDs. On the other hand, the risk of low-dose celecoxib, especially when used once daily, appears to be similar to that of non-users.
- The increased cardiovascular risk of all NSAIDs is, at least in part, explained by impaired kidney function, i.e. sodium retention, deterioration of cardiac insufficiency, and increase in blood pressure.
- Compared with traditional NSAIDs, selective cox-2 inhibitors may bring additional risk in that they exert prothrombotic effects that increase ischemic cardiovascular events, especially cardiac infarctions. This is most likely in situations where cox-2 expression of the intima of the blood vessel is increased (e.g. vascular surgery).
- Combining low dose aspirin with a coxib may decrease cardiovascular risk but in turn increase gastrointestinal risk.
- The adverse cardiovascular effects of NSAIDs can be decreased by intermittent use and by minimizing treatment periods and doses.
- The proper use of NSAIDs requires joint evaluation of both the cardiovascular and gastrointestinal risks of the patient.