

News from the International Symposium on Pharmacovigilance - London, April 26-28

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From Wednesday, April 26 to Friday, April 28 the international symposium “Pharmacovigilance of herbal medicines: Current state and future directions” took place in London. ANME visited this conference, as information on the views on regulatory and safety issues on various herbs was to be expected.

Adverse effect reporting systems

The major topic of the conference was the organisation of data collection systems including adverse event reports from herbal remedies. To the German audience this was mostly no news, as in Germany herbal remedies are subject to drug regulatory processes anyway, and a working adverse event reporting system is already in place. This is, however, not the case in most other countries where herbals are sold as food supplements or unregulated health products. Thus, the focus of the conference was clearly on the question how an underreporting of adverse events by herbals might be avoided, and how reporting systems can be constructed.

A large number of systems were presented, e.g. the adverse event database of the WHO, the Yellow Card System of the British MHRA, systems established by the BfArM, the EMEA, the ESCOP, the German producers of antroposophic medicines, the system installed by the Chinese drug regulatory authorities (perfectly structured and transparent, but all in Chinese!) etc. Most systems are installed in parallel and do not fully cooperate, mostly due to differences in terminology and coding. As the organisations partly communicate adverse effect reports to each other, an increase of duplicate entries and thus the danger of false signals is to be expected.

Still, all organisations claim that there is a considerable degree of underreporting, as most patients do not believe that herbs might be harmful. A number as high as 90% of underreporting was suggested. However, what was not discussed is the degree of underreporting from chemical entities. The high degree of underreporting was attributed to the work overload of general practitioners, which would in fact also apply to synthetic drugs. Our experience is that adverse events from chemical entities are often not reported when the possibility of such effects is already mentioned in the package leaflet of the corresponding product. However, there is no doubt that there is a need for improvement of pharmacovigilance systems, regardless of the nature of the products.

Drug quality and adverse effects

The major improvement of existing reporting systems respective acting on supposed signals was, however, not discussed. Logic would suggest to address the impact of quality as a factor contributing to drug safety. However, this is never done, although all examples of herbal adverse drug reactions discussed in the conference were in fact related to drug quality:

- St. John’s wort (*Hypericum perforatum*) interactions are clearly related to the content of hyperforin. Patients taking products high in hyperforin are at risk, patients with traditional products or regular extract qualities not artificially enriched in hyperforin are not. Several experts from the audience tried to raise this issue, but obviously there is no place for quality aspects in pharmacovigilance.
- *Aristolochia* and aristolochic acid are clearly recognized as the causative factors for Chinese herb nephropathia. However, the use of *Aristolochia* can be traced back to a substitution of the safe plant *Stephania tetrandia*, which has the same vernacular name, but is non-toxic. Still, there does not seem to be a future even for *Stephania* on the herb market.

- *Cimicifuga racemosa* (Black cohosh) has been linked to hepatotoxicity in a number of case reports (of doubtful quality). However, such effects are only known from poorly controlled products from countries where the sale is unregulated. As according to the presentations in London 97% of the raw material of Black cohosh is collected by wild crafting, the danger of substitutions and adulterations is high and should be countered by proper analytical controls. Such controls are established for companies where *Cimicifuga* preparations are prepared under the GMP rules applying for registered drugs. Again, the question of drug quality is not taken into consideration by the pharmacovigilance systems – problems with drug safety are directly related to the herb as such, and not to specific products.
- A striking example of bad quality presented in the conference was the business conducted by Panpharma in Australia. This producer was finally closed down by the regulatory bodies, based on fraudulent treatment of herbs and analytical protocols. The safety problems that resulted from the criminal acting of the company are, however, still linked with the herbs as such and not the specific quality of the products implied in the case reports.

In conclusion, the discussion of herbal drug safety can easily become highly artificial, especially when problems related to the bad quality of one specific product are instilled on all preparations containing this herb, regardless of their quality. A basic principle of pharmacovigilance is doubt, which can act both ways. Scientists would argue that when the culprit is identified, there is no more reason to suspect the plant as such. People involved in pharmacovigilance do not agree: As long as there is no proof that the regular quality of the plant does not and never cause the discussed kind of adverse effect, its safety must still be doubted. The magic word is “precaution”.

The precautionary principle

The problem with this line of arguments and especially with the “precautionary principle” is that a complete absence of any given phenomenon cannot be guaranteed scientifically. Science can only demonstrate effects, but never the absence of an effect. Therefore, pharmacovigilance can be abused by regulatory bodies for political reasons with no control whatsoever. Recent examples are the discussions on kava, St. John’s wort and Greater celandine (*Chelidonium majus*). Based on the argument of a negative risk-benefit ratio of any given herb a single adverse event can be sufficient to cause the ban of preparations from this plant all over Europe.

The benefit itself is defined by the outcome of modern clinical trials. Even though there is a huge number of clinical trials on herbals, almost all of them are not compliant with modern standards in clinical research (the question is, of course: how many chemical compounds are tested according to these modern standards, especially among the “older” drugs?). When only the most recent standards are accepted – which is currently the case with Kava and greater celandine – only a handful of plants would be attributed clinical benefits, and maybe not even those. With >90% of herbs falling under traditional use, and with traditionally used herbs by definition being used without a clinical proof of efficacy (otherwise they would be well-established), there is a constant threat that the plug might be deliberately and quite arbitrarily pulled on any given herb – all in the name of consumer safety. Whether the quality will profit, is highly doubtful, as grey trading channels cannot be effectively controlled, and the products sold through these channels are completely uncontrolled and as such potentially unsafe.

Figures outweigh causality

Another major problem with pharmacovigilance is the importance of figures. Numbers of case reports are in fact more important than causality assessments or the calculation of incidence rates. The WHO pharmacovigilance database contains a large number of entries which do not reflect causality. “Signals” indicative for potential problems are entirely generated based on numbers of case reports, not on assessments of individual cases. As was discussed in London, a signal based on case numbers instead of facts can be misleading.

The WHO currently has >3.6 mio. case reports of adverse events in total. A total of >41,000 cases involved herbals, 17,000 of which was use of herbals in mono-therapy. The small percentage of herbals in the total database might (according to WHO representatives) point to a certain extent of underreporting. However, an underreporting would also have to be expected for chemical entities, and would certainly not accumulate to extents that would shift the deduction of an overall very safe use to a critical threshold. I personally interpret the figures as a general proof of safety – the deduction of a potential problem from figures giving no real evidence that such a problem exists, and founding the argument on the mere suspicion that the figures might simply be too low mirrors a weird state of mind of the regulators. Again, an overregulation only leads to a decrease of quality, which then may cause problems in the sense of a self-fulfilling prophecy. Who protects the consumer from the consumer-protectors?

Current signal generation

The plants mostly involved in herbal adverse event reporting were *Hypericum perforatum*, *Ginkgo*, *Echinacea*, *Serrenoa*, *Mentha* and *Plantago ovata* – with figures of reports ranging up to 600/plant (for ginkgo). This would represent a very small risk, however, according to the speaker even the tiniest risk might be intolerable without a benefit standing against this risk. Currently, the WHO sees a signal for hypertension by *Cimicifuga* and *Panax ginseng* (based on single reports from three sources), but not by *Eleutherococcus senticosus*. WHO also detects a potential signal for white blood cell changes under *Hypericum perforatum* from approximately 5 sources worldwide. New discussions ahead?

Kava

In most presentations kava was not mentioned – deliberately, as it seems. I had the impression that kava makes the regulators uneasy, as if they knew exactly that the signal of toxicity they argue does exist might in fact be false positive. The topic of kava was even largely avoided in the presentation of Prof. Hagemann, former head of the pharmacovigilance department of the German BfArM and most responsible for the decisions taken against kava.

- In his only direct mentioning of kava he explicitly said that kava was traditionally used as a beverage and never in the form of extracts for the treatment of anxiety. Implicitly this reflects his opinion that kava has no effect, respectively the rather strange view that scientifically the effects of the aqueous kava drink must be separated from the effects of ethanolic extracts.
- Hagemann states that adverse effect reports are thoroughly examined by the staff of his department, taking into account the possibility of underlying diseases, proper use and quality. However, this is exactly what we found to be insufficiently addressed in the drug safety protocol, if ever addressed. Questions related to the differences in the quality of raw materials, and hints to other possible causes of the reported adverse events (e.g. underlying hepatic disease!) were never taken into consideration, and the line listings with tabulated adverse events prepared by the BfArM contains a high amount of factual errors – so much for the thorough assessment.

- The question of the alleged inefficacy was again raised, although not directly related to a specific herb. Hagemann said: “If there is no benefit, you have to take it off the market”. This reflects a general problem of pharmacovigilance in Europe: The definition of benefit and risk is far from being consistent. Whereas in the very same conference 80.000 causal case reports with Vioxx (also banned) were claimed to be in an acceptable range in view of the benefits millions of users experienced (less than 1 case report of stroke or cardiac infarction in 10,000 patients stood against an anti-inflammatory efficacy) the same moderate view is not attributed to kava (less than 1 case report of hepatotoxicity in 1,000,000 patients!). Here, the benefit is simply not accepted, despite the existence of >35 clinical trials and several positive meta-analyses with kava.
- Pinpointed to kava Hagemann stated in the discussion that the number of adverse effect reports (and thus the incidence) is less important than the severity of the adverse reaction. Hepatotoxicity of kava clearly outweighs the low number of reports (almost verbatim). The problem with this kind of argumentation (which is in fact not in accordance with the arguments of the WHO that numbers outweigh causality) is that it is entirely based on arbitrary judgement: What is an acceptable threshold of severity? Severe adverse events are linked to any plant or agent, and have to be expected for any plant or agent once in a while. The argument used by Hagemann demonstrates that in fact the question of incidence rates (the number of case reports with kava is by far lower than the natural occurrence of liver disease without any link to drugs or toxins!) does not count for the German BfArM.

As Hagemann has to defend his highly questionable decision on kava (there are liabilities at stake – the question of indemnation is still open!), a corrected view from him is not to be expected. However, the general attitude in the audience was one of disbelief, even from regulatory people from other countries such as Switzerland – even though these countries also banned kava.

Re-evaluations of kava

One of the reasons why kava was not mentioned by the representatives of the MHRA and the WHO was the pending review. In both cases I was told in discussions in the coffee break that the result of the review of the MHRA is to be expected within the next weeks, potentially already in May. Likewise, the review of the WHO seems to be almost finished, and will also be published in the near future.

In both cases, we may reasonably expect a much better view on kava than the one held by Hagemann/Thiele from the BfArM. Rumours from insiders say that kava hepatotoxicity might be seen as a consequence of a quality problem, which might open us a way to demonstrate that the quality issue has been effectively solved by the kava exporting states of the South Pacific.

Requirements for CTDs

Until 2011, all herbs currently on the market which are not in the process of drug registration will have to be registered under the rules of traditional use. Drugs not being registered after that date cannot be traded any longer. Speakers in the conference pointed to the basic necessities:

- An application for “traditional use” in any EU member state of through the EMEA, which in the case of the EMEA requires the creation of a monograph, and in the case of a national registration a full documentation by the producer. In both cases work will have to be done to compile the necessary documentation. I was again told in London that London lacks the personnel and the funding to properly perform its task to create lists of traditionally used plants. Already now it is quite obvious that the EMEA will not be able to provide much support for a high number of herbs. Producers will have to act, and to act soon, or otherwise they will lose their market.
- Any registration of a traditional herbal product will have to be accompanied by a quality dossier according to CTD (Common Technical document) part 3.2. This part of the CTD includes sophisticated analyses on the levels of the herb, the preparation and the finished product. The major topics to be addressed are identity, purity (e.g. lack of adulterants, mycotoxins, heavy metals or microbiological contaminations) and stability. Traceability of the herbal raw material is also a major topic. All tests have to be validated. Again, producers will have to act soon, especially since stability testing takes up to 5 years. Products without a CTD will not be accepted on the market any longer.

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