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ARTICULO DE OPINION

Hazardous drugs: new challenges, new opportunities

Medicamentos biopeligrosos: nuevos retos, nuevas oportunidades

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Abstract:

Occupational exposure to hazardous drugs can cause harmful effects on health professionals and several protective measures must be taken. Nevertheless, classification of hazardous drugs is not the same in all the published repertoires and the termi- nology is still confusing: hazardous drugs, biohazardous drugs or risky drugs are terms improperly described and can define very different drugs with a very different hazard profiles.

In Spain, there is not an updated official list of hazardous drugs, and healthcare professionals must consider and follow other published lists. In our opinion, it is mandatory to do a consensus among these professionals, administration and labor union organizations in order to clarify some conflicti- ve questions not only in healthcare settings but in investi- gational and academic scenarios too. These multidisciplinary groups should be involved also in teaching new and non-ex- perienced personnel and in the knowledge reinforcement for the experienced ones.

Keywords: Hazardous drugs, Occupational hazards, NIOSH, Update guidelines.

Resumen:

La exposición laboral a medicamentos biopeligrosos puede causar daños a la salud en los profesionales sanitarios expues- tos, por lo que deben tomarse medidas protectoras. Sin em- bargo, la clasificación de estos medicamentos no es la misma en todos los repertorios y listas publicados, y la terminología sigue siendo confusa: medicamentos peligrosos, medicamen- tos biopeligrosos o medicamentos de riesgo son términos que no definen bien el concepto que se quiere transmitir, y agrupan sustancias muy diferentes, con perfiles de riesgo también muy diferentes.

En España no hay una lista oficial actualizada de medicamen- tos biopeligrosos, y los profesionales de la salud deben consi- derar y seguir otras listas publicadas. En nuestra opinión, sería necesario establecer un consenso entre profesionales, Admi- nistración y organizaciones sindicales para clarificar y definir las distintas cuestiones planteadas, no solo en el medio sanitario, sino también en otros escenarios (investigación, estructuras docentes), incluyendo la formación e información de todo el personal implicado.

Palabras clave: Medicamentos biopeligrosos, Riesgos laborales, NIOSH, actualización guías.

Recently we have had the opportunity to read some news in the written press about the controversy crea- ted by the handling of certain drugs, and its potential consequences for the health of professionals involved. This news has caused an upheaval within the healthcare setting, and has forced the main players (professionals, labor union organizations, administrations) to review the reality we are currently facing. The analysis of this

reality has revealed some aspects which require discussion and consensus by the scientific community and which, in our opinion, need to be clearly pointed out.

A review of bibliography shows that occupational exposure to certain drugs can lead to the development of acute [1-2] or chronic [3-4] adverse effects, such as skin rash, reproductive disorders [3] or potential chromosomal alterations [5]. The effects mentioned, as well as in the case of exposure to ionizing radiations, are considered stochastic effects, that is to say, these are effects that *might* appear, but not necessarily in all cases. We can only say that there is certain likelihood, higher or lower according to each case, that these effects will appear. To determine a direct causal relationship between the exposure to these drugs and the development of neoplasia or other effects on health will be very difficult, logically, due to the multifactorial nature of this type of pathological processes; moreover, there are no ade- quate diagnostic or prognostic biomarkers. Faced with this circumstance, it would be advisable, according to caution criteria, to follow the principle called ALARA (*As Low As Reasonably Achievable*) regarding the exposure to this type of molecules. However, nobody can guarantee that a person who has been exposed during their entire working life to this type of substances, either using or not the protection measures available, will develop a pathological process associated with exposure; and this makes it difficult to determine a rational level of awareness in terms of the measures that healthcare professionals must take at the time of handling these agents, both in the positive sense of training, protection, and acquisition of the necessary technical abilities, and in the opposite and negative sense of exaggerated public alarm, and what we could call "psychosis of risk".

We must add to this fact the issue of the termino- logy that should be used to classify or categorize this type of drugs. In our specific case, and being aware of terminological and semantic limitations, we decided to adopt the term "*fármaco biopeligroso*" (FBP), which represents an approximate translation from the English "*hazardous drug*". This term was first used in the 90s by the *American Society of Hospital Pharmacists* (ASHP) [6], and subsequently adopted by the *National Institute for Occupational Safety and Health* (NIOSH) in 2004, which considered as such all those drugs that had shown in studies with animals or humans one or more of the fo- llowing characteristics7:

1. Carcinogenicity
2. Teratogenicity or other toxicity for development
3. Reproductive toxicity
4. Organ toxicity at low doses
5. Genotoxicity
6. Drugs with toxicity structure or profiles which are similar to other existing drugs considered hazardous.

The term "hazardous" seems to exclude the chemical risk associated with these drugs; therefore, terms such as "dangerous drugs" have also been considered, but these might be too wide and alarming (Is digoxin not dangerous?), or "risk drugs", which might lead to confusion my mixing the concepts of risk for patient (associated with the use of drugs with narrow therapeutic margin and/or severe adverse effects), and risk for the person handling them. We are aware that this is only a theoretical aspect, but words are powerful, and it is necessary that the whole scientific community can use the same name for the same type of drugs and, consequently, the definition of what is involved will be clear.

From a technical point of view, we should ask ourselves if the definition and the characteristics determined by the NIOSH in order to consider a drug as hazardous are really adequate. Even accepting the stochastic model of risk (and therefore, not dose-dependent) for these substances, it will be difficult to identify, for example, the teratogenic ability of phenytoin or fluconazole administered orally or parenterally at therapeutic doses, with the potential aerosols generated after the reconstitution and administration of these medications within a health- care setting. The classification of risk by the *International Agency for Research on Cancer*(IARC) is even more disturbing and generates more confusion, when it assigns to the extract of

Aloe vera leaves the category of *poten- tial* carcinogenic agent in humans (class 2B), the same as phenytoin, but to a lower extent than the intake of red meat, which has been classified as a *probable* carcinogenic agent (class 2A), or processed meats, which are considered carcinogenic (class 1) [8].

The lack of a formal list, approved by consensus, of drugs which should be handled with special measures of protection by patients, caregivers, and healthcare profes- sionals, supported by the European Medicines Agency (EMA) or the Spanish Agency for Medicines and Health Products (AEMPS), as well as the lack of specific informa- tion in the product specifications of many of these drugs, leaves the responsibility and the final decision making in the hands of the professionals involved in the pharmaco- therapeutical circuit for this type of substances, in terms of accepting or not the protection measures for handling recommended by the scientific literature available. There is a Technical Note on Prevention published by the Spa- nish National Institute of Security and Hygiene at Work (*Instituto de Seguridad e Higiene en el Trabajo* (ISHT)) in 2006, the well-known NTP 7409, which establishes a classification of the main cytostatic compounds and associated products, and it reflects, when available, the classification by the IARC for the same products. Howe- ver, this NTP 740 has not been updated since its publica- tion, and therefore it does not include those new molecules that meet the criteria to be considered hazardous drugs, while it includes some others which have been excluded from the lists by the NIOSH. This fact can gene- rate a disparity in terms of hazardous drug management according to each healthcare centre, only determined by the different criteria followed by those professionals res- ponsible of determining which measures to use and for which drugs should these be implemented.

It might not be necessary to write a list of Hazardous Drugs, and the list established by the NIOSH could be used. This list includes a majority of antineoplastic drugs, but also antivirals or hormonal medications, among others [7], and it is periodically reviewed (the latest reviews were conducted in the years 2012 and 2014). This last review [10] determines a new classification of Hazardous Drugs into three groups:

1. Group 1: Antineoplastic drugs.
2. Group 2: Non-antineoplastic drugs that meet one or more of the criteria established by the NIOSH for Ha- zardous Drugs.
3. Group 3: Drugs which can cause reproductive altera- tions in men and women trying actively to conceive, pregnant women or those actively breastfeeding.

This new sub-classification of Hazardous Drugs does not clarify any of the aspects we have mentioned befo- re; on the contrary, it generates new practical doubts: Should the same general protection measures be imple- mented for handling all Hazardous Drugs, regardless of the group they fall into? How should we act with drugs from Groups 2 and 3? The fact that a great proportion of the healthcare professional staff is formed by a majo- rity of young men and women of childbearing age will make it difficult to implement individual measures for protection and adaptation of the work setting.

It is clear and generally accepted that Group 1 drugs must be handled in a centralized manner in the Pharma- cy Units, applying the collective and individual measures of protection which are necessary and recommended by the main scientific societies [7], [11 - 15] and by current legis- lation [16 - 17]. The presence of contamination by cytostatic agents in the healthcare work setting has been demons- trated in many international studies [18 - 20]. In our country, there are currently very few experiences of this type, but there are on-going studies on this subject, the outcomes of which are not expected to be different from those already known [21]. This demonstrates that occupational exposure to Hazardous Drugs is a reality, and there is a high likelihood of contact by healthcare staff with these agents, if no precautions are taken. There are no studies available so far about the consequences on health from this contamination, but these will probably become avai- lable during the next years.

But this does not end our doubts. Occupational exposure to Hazardous Drugs can occur when aerosol is caused or dust is generated during their handling and preparation, while cleaning up spilled liquids, or by tou- ching surfaces contaminated during preparation, admi- nistration, or disposal of these agents [7]. The lack of adap- tation by the industry of some of the formulations for this type of drugs as ready-to-administer preparations will force the Pharmacy Units to handle them.

In the case of intravenous formulations, the adapta- tion of vertical laminar flow hoods in controlled settings seems to be enough to protect the healthcare profes- sional. Even so, and taking into account the previously mentioned ALARA principle, some additional measures of protection should not be disregarded, such as roboti- zation [22] or the use of closed drug transfer device systems. The ISHT has published a new Technical Note on Pre- vention (NTP 1051) [23], which establishes that one of the sources of contamination for working surfaces is the ge- neration of aerosols during the process of preparation of antineoplastic drugs for their subsequent administration. In order to reduce this contamination, it is recommended to use closed systems and robots during the preparation phase. The requirements that any device must meet in order to be considered closed are also included.

However, the adaptation of the doses of solid phar- maceutical formulations can represent a problem, due to the saturation of the hood filters and the lack of adequate handling devices. This compels us to consider new handling methods, which have not always been studied from the point of view of the handler's safety.

It seems clear, then, that "we have laws, but lack regulations". In our opinion, it is necessary to turn recommendations into rules: to define clearly which substances must be considered hazardous and how these must be handled, which is the adequate frequency to update these lists, how to solve structural and staff needs in many Hospital Pharmacy Units at the time of approa- ching Hazardous Drug preparation, and how these lists must be defined. The work by multidisciplinary groups of professionals, with involvement by labor unions and experts in occupational health and safety would be un- doubtedly helpful in this task, in order to define and coordinate these matters not only in the healthcare se- tting but also in teaching or research scenarios, where this type of substances are often handled too. On the other hand, conducting studies on the situation at a na- tional or supranational level would allow us to know the degree of exposure in each scenario, and the measures of protection used in each one.

The existence of these multidisciplinary groups of experts with recognised prestige would also allow addressing the training of professionals, and facilitating an im- partial distribution of information to the media and the society, staying away from interested demagogies and an exaggerated alarmism.

At the same time, the adaptation of healthcare circuits and the increase in workload for the Pharmacy Units is a fact that must be taken into account by the authorities in each centre. A staff formed by qualified professionals who have received adequate training is more than essential if we want to preserve the levels of quality required, and the safety for patients and handlers. Aspects such as periodical training and evaluation are key factors in order to achieve the objective in a satisfactory way; and this objec- tive should be none other than the improvement of overall safety in drug management within the healthcare setting.

Conflict of interests

The authors hereby declare that there is no conflict of interests.

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