Global recurrent classifications in experimental and clinical pharmaco-toxicology*

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Premise

The Greeks were already aware of the fact that a farmacon could be both a drug and a toxic substance (in cauda venenum). However, current pharmaco-toxicology (PT) has not yet been able to establish definite risk / benefit ratios related to drug administration: this concerns both the recipients, including the population, individual subjects and organisms, complex analytical or kinetic structures distributed over time, and dynamic structures, and the time frame involved (simultaneous, mixed). Especially on these critical issues I have reserved to the Accademia a number of dense and original contributions, especially of methodological nature, some of them quite extensive(1-7).

These contributions have been published only in our Proceedings/Papers, the last three involved communications presented at least 12 years ago. Given the time elapsed, I feel a brief update, at least of some of them, is now in order, also in view of the possibility of their diffusion in print in the near future.

Even the continuously evolving PT sciences, whose evolution is affected by crises related to the ability of the models themselves, and of the experimental tests, to be falsified, cannot escape the repeated classification of their complex nature, albeit consistently dependent on their individual, even isolated concepts of individual and general knowledge; this presents indefinite aspects of debates of educational and professional responsibility that is first and foremost personal, making reference to ethics values that are only occasionally enforced in national and regional regulations. For instance, it is essential for professional training in biomedicine to collect consistently and preserve completely all available information from animal experiments – as in standardized multidimensional screening.

Though contrasted this is essential information, like that of clinical trials, that cannot be confined to traditionally controlled studies, but must be extended to all possible cases justified by the diagnostic, preventive, therapeutic and rehabilitative interventions applied. The IT revolution, together with the revolution related to the most advanced knowledge domains of the analytical chemical, physical and epidemiological theories, has enabled its dynamic structuring of feasibility. Also in this context the vocation of grenzgebiete, the need to delve deeper into shared borders, should not be neglected. Those interested can find the relevant bibliography also in the newer references reported here(8-15).

Recent Contributions

Over the last few years all toxicology-related research avenues have been inexplicably and unjustifiably abandoned by this university and regional hospital (despite, but certainly not by, ourselves). The resulting damage has been severe and irreversible, affecting persons as well as the institution. Nonetheless in the framework of the experiments of the first substitutive Projects (Cf: Chancellor n 8791, 1.4.2009) financed in the 2007-8 budgets, it has been possible to address only our own permanent research lines, objective autoclassification, based on the adverse reactions and effects database, an international network begun here and encompassing today 141 national reference centres of the current 137 participants.

In addition (and very much unlike the literature\(^{(16)}\), where the issue has only exceptionally been addressed), thanks to the courtesy and generosity of the colleagues of the Uppsala International Collaborative Centre, our original software\(^{(20)}\) – subsequently distributed to the 141 Centres, has enabled analysis of the 201,928 adverse events and reactions reports relating to the 73 contrast agents included in the conventional classes, sent to the WHO bank over the first 40 years of its foundation\(^{(20)}\).

Their significant autoclassification profiles were examined according to the original standardized model, i.e. as divided into the **seven most frequently reported groups in the two 20-years periods**\(^{(17-18)}\) **as well as grouped** into the chemico-pharmaceutical classes of 30 ionic and non-ionic iodinated agents (ATC Vo8A, subclasses –A, -B, -C and –D)\(^{(20)}\), used as radiographic agents; 10 paramagnetic agents for MRI enhancement (subclass ATC Vo8C-A)\(^{(19)}\), and their biosimilars\(^{(21)}\); finally, for the same products, the 4,436 reports sent from Italy were compared to the 181,744 sent by the other countries\(^{(22)}\).

Current Conclusions

The diagnostic products employed in radiology should not give rise to direct dynamic benefits, but present risks of rare complex toxicities such as nephropathy (CIN) induced by iodinated agents and nephrogenic systemic fibrosis (NSF) associated with gadolinium-based contrast agents (GBCAs), which due to their specific clinical effects were not included in our analysis.

As regards the other adverse reactions, i.e. toxicity arising at the normal dosage, the reasons and/or criteria for their subdivision into classes and subclasses are principally related to physical and chemical similarity of chemical-pharmaceutical nature, or to the onset of (never sought) individual events and/or reactions even of a favourable nature, or else identification of local or systemic organic disorders (SOCDs), according to the ATC, the most widely accepted classification, approved by the WHO, which is based on anatomical, therapeutic and chemical criteria.

It must be noted that the significant projections detected in our analyses, significant in all cases\(^{(17-20)}\), matched neither the known chemico-pharmaceutical criteria nor those adopted for the ubiquitous use of ATC classes. This suggests the urgent need for a review of their suitability and re-examination of the need to maintain them despite their lack of robustness, and consequent precariousness. Possibly another paradigm. Specific national trends have also been detected\(^{(22)}\), as have highly significant distinct features among the reference products and their salts, which are still and erroneously considered as biosimilars and equivalent under all profiles\(^{(21)}\).

Developments

The multi-author paper published in Science\(^{(23)}\), preceded by a presentation in the Perspective in the same issue\(^{(24)}\), regarding the new MINE Statistics has restored confidence in the ongoing exchange between the MIT, Harvard and Oxford groups\(^{(25)}\), which is in line with the Anglo-Saxon tradition of letting researchers work after the local retirement age: to prevent teaching, honed and developed with passion and with new enthusiasm, from being
obiterated and allow it to continue to provide its contribution. Besides this project dates from September 1, 1991, the date when the Italian Health Ministry Study Center approved the outcome of the First Convention January 13, 1989 on “Research addressing the development of a statistical-modelling program for the detection of consumption and the evaluation of benefits and resources of some groups of drug using data of the WHO cofounded Uppsala data bank”, whereas the continuation, besides the evolution reported here, already financed with, has mythically been lost ... along the way: one is reminded of the citations of Tolstoj and Vonnegut in E no?.

Citations

(20) Bradu D., Rossini L., Contrast agents – full list of the 30 iodinated products for which reports have been sent over the first 40 years of the WHO Pharmacovigilance system, subdivided into two 20-year periods. Fourth WHO-ITA / ITA-OMS 2010-2011 contribution on the 30 basic aggregated WHO System-Organ Class Disorders (SOCDis) and Suspected Adverse Reactions and Event preferred names (SADRs). Pharmacologyonline Newsletter 2, 701-836, 2011.
(21) Bradu D., Rossini L., Biosimilar branded iodinated contrast agents related to the largest number of reports to the pharmacovigilance system over the first 40 years of the Programme. Fifth WHO-ITA / ITA-OMS 2010-2011 contribution. Pharmacologyonline Newsletter 2, 929-962, 2011.
(22) Bradu D., Rossini L., 4,436 reports from Italy, accepted in the WHO-UMP Collaborating Centre Thesaurus V5 181,744 globally collected reports from other participating Countries of same 33 monitored contrast agent-products over the first 40 years of the Programme. Sixth WHO-ITA / ITA-OMS 2010-2011 contribution. Pharmacologyonline Newsletter 2, 1140-1160, 2011.
(27) Cf: CS/413/FARM/93/AG/1526 del 26.11.1993, Oggetto: “Ricerche di aggiornamento di studio di modalità” autocallassificative per il confronto di profili di reazioni avverse di gruppi di farmaci, come segnalate alla Banca internazionale O.M.S., Uppsala Ginevra”, Responsabile lo scrivente, ove si comunica all’ Universita’ degli Studi di Ancona, Istituto di Medicina Sperimentale e Clinica, Via Ranieri, Monte d’ Ago, 60131 Ancona “che in data 22 ottobre c.a. l’ On Ministro, in conformità al parere espresso dal Comitato di Coordinamento di questo Centro Studi, ha approvato la ricerca in oggetto, che sara’ affidata in convenzione a codesto Istituto, per un compenso di lire 60 milioni”.