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The Role of the Clinical Pharmacologist in the Management of Adverse Drug Reactions

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Abstract

The classical definition of clinical pharmacology is the study or the knowledge of the effects of drugs in humans. The activities of a clinical pharmacologist can vary from country to country, usually ranging from involvement in clinical trials, especially fundamental pharmacodynamic studies, to studies of pharmacokinetics and drug metabolism, to pharmacogenetics. Most clinical pharmacologists outside industry are in hospitals or university hospitals and research centres. In addition to research, this implies teaching of clinical pharmacology, and interacting with other medical staff: in the field of research, giving advice on clinical trials methodology and often managing a therapeutic drug monitoring centre. Some clinical pharmacologists have clinical departments with beds or consulting offices.

Can there be another role for the clinical pharmacologist that would increase his or her usefulness for the medical community? Adverse drug reactions (ADRs) are remarkably complex events, related to drug effects, patient characteristics (background diseases, genetics), and drug/disease interactions.

Evaluation of ADRs requires understanding of drug mechanisms and interactions, and of disease diagnostics, especially in the discussion of alternative diagnoses. This implies expertise as a pharmacologist and a clinician. In addition, because not all adverse reactions or interactions are in the Summary of Product Characteristics, and because problems arise long before they report in the literature, it is necessary for the clinical pharmacologist to have knowledge of ongoing regulatory processes, in addition to having access to the published literature. Helping clinicians cope with individual patient problems will also improve the clinical pharmacologist's integration into the healthcare process.

1. Background

Adverse drug reactions (ADRs) are a major medical problem, accounting for 3 to 10% of general practitioner consultations, hospital admissions and excess hospital days.[1,2] They result in the death of several thousand patients each year[3,4] and can represent up to 15 to 20% of a hospital's budget.[2,4] These figures have been known for the last 40 years, and they have not changed much since, despite better knowledge of drugs and better understanding of their effects and interactions, both positive and negative, and a growing knowledge of the existence and magnitude of the problem.

There are many participants in the issue of ADRs: the patient, the prescriber and the dispensing phar-

macist, who are directly involved, and also the environment around that basic triad: hospitals, teachers, specialists, regulatory authorities and drug manufacturers. Within this second circle of defence, there is the clinical pharmacologist, who has a pivotal role in the management of ADRs. This role is still often underestimated and clinical pharmacologists underused.

This article is a review of the role of clinical pharmacology and clinical pharmacologists in the management of ADRs, initially prepared for presentation at the September 1999 meeting of the European Society of Pharmacovigilance (ESOP) in Ankara, Turkey. It is written by a clinical pharmacologist convinced of this role and therefore very partial. No doubt others will plead for the primordial role of other professional categories in the management of ADRs, of the primacy of regulation, or the importance of lawyers or consumer organisations. My knowledge is restricted to clinical pharmacology and biased by 20 years of work in the field of ADRs. This view is also influenced by long term experience with the French medical and pharmacovigilance systems. Readers may need to interpret it in the light of their specific national systems.

2. Classification of Adverse Drug Reactions

ADRs are multifaceted. To simplify greatly, using Sir Michael Rawlins's classification,[5-7] they can be divided schematically into major categories: type A [as in augmented, or attendu (expected in French)]; type B (as in bizarre); and type C (as in complicated).

Type A reactions are the pharmacologically-determined reactions that are dose-dependent and will be found in susceptible patients at therapeutic doses and ultimately in most or all patients as dosage is increased. The frequency of type A reactions is such that they can evolve into therapeutic indications. For example minoxidil, a vasodilator evolved from being an antihypertensive drug with hair growth as an adverse reaction in young women to a treatment for baldness in men, with an attendant risk of hypotension or interaction with antihypertensive drugs.

These type A reactions are by far the most frequent type,[2,8,9] and can be observed in as many as 25 to 40% of patients (or up to 100% for cancer drugs). Once they are known and included in product information, they are usually not the object of regulatory activity, are generally considered as being the ransom of progress ('all drugs are dangerous, some are also useful') and are rarely, if ever, reported. However, they represent the vast majority of the serious drug reactions. Most could probably be avoided and/or anticipated.[10,11] They represent the real risk and cost of drugs to society.[4] The drugs involved are well known: anticoagulants, anticancer drugs and nonsteroidal anti-inflammatory drugs (NSAIDs) are at the forefront.[8,9]

These adverse reactions are not amenable to spontaneous reporting, and insisting on their systematic reporting would be the best way to choke any system to death with trivial information. In France, there are an estimated 10 to 20 million consultations yearly by patients with ADRs.[12] These reactions can really only be studied by systematic pharmacoepidemiology studies, or better still by large scale randomised clinical trials. These are rarely done – why would a drug company sponsor a trial that could put their drug at risk when not doing anything is generally safe? Public health systems and insurance companies, who are the ones who really have a stake in knowing, usually do not have the funding to support multimillion dollar trials of unappealing topics (e.g. a long term prospective evaluation of real bleeding rates with different NSAIDs for osteoarthritis or common pain).

Type B reactions are the rare, idiosyncratic adverse reactions, usually immunoallergic, that are often spectacular and frequently reported, such as toxic epidermal necrolysis, acute severe hepatotoxicity, renal failure, blood dyscrasias, anaphylaxis, etc. Such reactions lead to extensive discussions on risk, and can result in drugs being taken off the market for risks that are in essence very low, but are highly visible. These reactions are so rare as to be accessible only by spontaneous reporting, by some

of the more arcane pharmacoepidemiological methods, such as case-population studies,[13] or to unrealistically large cohort studies.

The distinction between type A and type B is everchanging, with more reactions being classified as pharmacological rather than idiosyncratic as pharmacogenetics progresses, but the A versus B distinction remains useful for teaching purposes.

To these first 2 categories can be added a third one, not initially described, that is called C by some. This is the increase in frequency of an event that is expected in the treated population, such as sudden death in cardiac patients treated for arrhythmia, or suicide in depression or schizophrenia. A type C reaction may also manifest as increased rates of a 'spontaneous' disease (e.g. cancer), and may involve effects in a subsequent generation. This will rarely be reported, and will usually be a disagreeable discovery in studies designed to demonstrate something else (e.g. the Cardiac Arrhythmia Suppression Trial, which revealed an increase in mortality due to arrhythmias in patients treated with antiarhythmic drugs.[14]

The consequences in terms of management of these different types of adverse reactions appear obvious. Type A reactions must be taught to prescribers, so that they can be anticipated. Prevention is at the individual patient-prescriber level. It may be possible to identify patients at risk, in whom certain drugs should not be used. Additionally, clear public health measures need to be taken beyond just changes in drug labelling. For example, NSAIDs at anti-inflammatory dosages are a major cause of upper gastrointestinal bleeding[3] and will probably be mostly replaced with lower risk, but much more expensive, selective cyclo-oxygenase-2 inhibitors within the next few years. It is not widely recognised that anticoagulants are involved in 3 times the number of gastrointestinal bleeding deaths as NSAIDs. Deliberate paracetamol (acetaminophen) overdose is the leading cause of hepatic transplantation in most industrial countries, but paracetamol is still available in drugstores in the US in 500-tablet containers (representing 25 times the fatal dose).

Type B reactions need to be tracked, identified, quantified and put in perspective. Prevention is usually in the realm of regulatory decisions, since almost by definition prevention at the individual level is impossible (at least as long as the eventual causal gene has not been identified and detected or treated). If a risk–benefit assessment on a single reaction is often quite easy, taking a global view of the multifaceted advantages or risks of a drug, along with all the other drugs in the same field is exceedingly difficult. Progress is being made, however, in the risk–benefit analysis process, under the auspices of the Conference for the International Harmonisation of Medical Sciences (CIOMS).[15]

The management of the adverse reaction can therefore be envisioned at the individual patient level, and at the population level. At the patient level, management can be understood to include managing the patient with a drug-induced reaction, to minimise harm, or at best prevent the ADR. It can also be understood to mean the reporting of the case to the proper authorities for recording and evaluation of what the individual case represents for the population risk. At the population level, management of ADRs implies regulatory processes, resulting in changes in the information content or the marketing status of the drug (e.g. restrictions on use or suspension of the licence).

3. Is The Need for Management of ADRs Fulfilled?

This question is very difficult to answer. There is a general lack of studies on the management of ADRs at the individual level. One poor measure could be the rate of hospital admissions for ADRs. Despite all advances in the understanding of pharmacology and drug reaction mechanisms, these hospitalisation rates have not changed much over the past 40 years.

In different countries the need for ADR management may be fulfilled by different structures. The tendency is to have 2, often unconnected, systems.

One is a central drug regulatory agency that receives reports and makes regulatory decisions, often with the help of experts in the therapeutic field,

pharmacologists, pharmacists or clinicians. These experts, however, may not always be trained in the actual problems of pharmacovigilance, if they are not involved in the daily assessment of reactions and alerts.

On the other hand, there is often a strong local or hospital-based information system, usually manned by pharmacists, or sometimes by pharmacologists. If these are not involved in the regulatory processes, they may not always be aware of ongoing problems or alerts, and information retrieval or reporting may not always be optimal.

4. Clinical Pharmacology and the Clinical Pharmacologist

Clinical pharmacology is the study of the effects of drugs in humans.[16] This covers metabolism and pharmacokinetics, but also pharmacodynamics, exploration of mechanism of action and effects. Depending on countries or circumstances, it may also include clinical demonstration of therapeutic efficacy and effectiveness, and large scale postmarketing studies, all the way to pharmacovigilance, drug utilisation, pharmacoepidemiology or pharmacoeconomics (societal pharmacology).

A clinical pharmacologist has a medical diploma (MD), clinical experience and pharmacological training. The term MD may be considered generically to cover all diplomas that give an individual the right to practice medicine in humans. Clinical pharmacologists are found mainly in universities, in industry, in regulatory authorities and in hospitals. The activity of clinical pharmacologists is teaching in medical schools, research in the public or industry fields, regulatory activities, and hospital activities.

Teaching includes teaching pharmacology to medical students, usually focused mainly on drug activity (pharmacodynamics), drug disposition and pharmacokinetics. This gives access to medical students at an early age, when they are still impressionable and ready to be imprinted with the fundamentals of the pharmacological approach to prescribing (rather than the 'cookbook' approach they may tend to learn later on). Early exposure of future physicians to clinical pharmacology and the clinical pharmacologist also facilitates future feedback. This may be reinforced by regular continuing medical education opportunities.

Research can be fundamental (exploratory or problem-solving) in a university setting, or regulatory-driven (to ensure proper research and timely registration of new drugs) in the industry. It is traditionally focused on studies of pharmacokinetics and metabolism, or of pharmacodynamics, increasingly including pharmacogenetics, usually in healthy volunteers. In France, no study of drugs can be done in healthy volunteers (i.e. studies without direct individual benefit) without the participation of a clinical pharmacologist.

Hospital functions of clinical pharmacologists vary from country to country, and can sometimes overlap with clinical pharmacy. They could include the management of a pharmacokinetics (therapeutic drug monitoring) laboratory, or a biological toxicology unit, patient dose management or counselling. Clinical pharmacologists may also be involved in hospital activities such as formularies or clinical research.

Finally, clinical pharmacologists are involved in regulatory approval and postapproval processes, either by being part of the process as assessors (as at the US Food and Drug Administration) or by participating in expert review boards or committees (as in France or the UK).

As we will see, this places the university- or industry-based clinical pharmacologist at the centre of the ADR management process.

5. Role of the Clinical Pharmacologist in the Management of ADRs

The clinical pharmacologist has by definition a dual training, in clinical science and in pharmacology. Additionally, a modern clinical pharmacologist will often be trained in statistics and epidemiology. The clinical pharmacologist's involvement in ADR management should be envisioned at the individual patient, and societal, level.

At the individual patient level, the clinical pharmacologist will be involved in management of the

patient with a drug-related problem and in gathering information on the case for reporting (assisted reporting).

The clinical pharmacologist will be involved as soon as the physician contacts the local (or regional) department of clinical pharmacology or regional pharmacovigilance centre for advice. Such resources already exist, either purely as information resources, usually called drug information centres, or as those more oriented to ADR monitoring and management, usually called regional pharmacovigilance centres.[17-22] Such centres exist all over Europe, and in fact in most countries. Their involvement in regulatory surveillance networks was institutionalised in France in the 1970s[23] and other countries have since followed suit.[24] In other countries, such centres are independent from the regulatory authorities, but perform mostly in the same way.[25]

The question or problem can range from a request for advice regarding drug administration, or the choice of a drug in specific circumstances such as pregnancy, to a call for help in managing complex clinical problems where the treating physician suspects a drug is involved.

The response can also range from the purely informative, possibly modulated by feedback to focus the question, to full-scale interaction in the management of the case, including recommending diagnostic or therapeutic procedures. Such advice can be purely neutral, based on the literature or knowledge of ongoing problems or it can be part of a more proactive approach, with the clinical pharmacologist taking an active part in the resolution of the drug-related problem. There may also be a proactive, preventive approach, when the prescriber approaches the clinical pharmacologist with a question concerning prescribing choice (e.g. in the case of a pregnant woman).

The clinical pharmacologist has a unique insight into the possible mechanism of the putative adverse reaction, the underlying or concomitant diseases, and the possibility of drug–drug or drug–disease interactions. In addition, the well-connected pharmacovigilante (a person involved in pharmacovigilance activities) will know of emerging problems long before they are published in the literature. The interaction will, therefore, be more fruitful, with the clinical pharmacologist being able to give sound advice to the prescriber, and at the same time improving the quality of the data on individual cases, such as suggesting laboratory tests or the order of drug withdrawal, or an experimental approach to solve more complex problems.

Knowledge of ongoing problems through participation in regulatory processes or advisory committees may also help to identify suspect drugs the physician may not be aware of as suspect, because the risk is not yet public knowledge. Having early access to patients can also help solve problems such as those related to drug withdrawals, which are often attributed to a newly introduced substituted drug. For example, a cause of seizures in hospitalised elderly patients is withdrawal of benzodiazepines, that the patients were not always aware they were taking, at admission. How often have these been attributed to the drugs given to treat whatever problem the patient was hospitalised for?

The diagnosis and management of ADRs is really a clinical specialty, unfortunately not yet recognised or licensed. Some of the clinical pharmacologists have specialised consultations, for general drug problem-solving, or for more specific problems such as drug choice and use during pregnancy.

Ensuring that the prescriber knows of such a resource can be difficult. Older practising physicians are not always aware that drugs are associated with adverse reactions, or what to do if they see or suspect an ADR, and it is not always easy to teach them to utilise the clinical pharmacologist. As already mentioned, this is where the clinical pharmacologist involved in the medical curriculum has a distinct advantage. Doctors will more readily contact the pharmacologist they know from their university years than a distant administration, especially if they are told that such a service is free and considered part of their training.

After all, compared with anatomy which only slowly evolves, pharmacology is constantly being

updated, and most drugs a prescriber uses were not available when they went through medical school. Moreover, information on existing drugs is constantly evolving. Thus, medical students cannot just be left to fend for themselves and find whatever information they can or rely on what the industry feeds them, but need to have some kind of follow-up available. Each contact will also be an opportunity to provide some general ADR prevention advice. This of course is augmented by participation in local or regional continuing medical education events.

Additionally, through participation of clinical pharmacologists in hospital and general practitioner formulary boards, further prevention of ADRs can be managed by the selection of drugs that are not only cost effective but also safer.

Involvement of the clinical pharmacologist in national regulatory networks provides a dual advantage: the patient receives better advice and the system gains better case reports. A case that involves the clinical pharmacologist will contain more pertinent information. Additionally, prescribers will tend to call the clinical pharmacologist for those cases which they don't understand or cannot quite manage, where they are uncertain as to the role of drugs, or of which drug is really involved. This is a different set from those that are reported 'spontaneously', which are more commonly cases where causality is certain, at least in the physician's mind. Thus, these cases that involve the clinical pharmacologist tend to be more unusual, or more severe, i.e. the ones the surveillance systems really want to know about, rather than yet another report of a well-known reaction.

Additionally, these unusual cases can provide good data for publications and leads on mechanistic research hypotheses or new treatment indications.

6. Alternatives to Clinical Pharmacologists

What are the alternatives to clinical pharmacologists? For many of the clinical activities, the place of the clinical pharmacologist could be taken by the clinical pharmacist (e.g. for dosage adjustments), by statisticians and clinicians (for clinical trials), or by epidemiologists (pharmacoepidemiology). However, there is no replacement for the clinical pharmacologist in pharmacovigilance. Pharmacovigilance in the sense used in this article is not just body-counting. It is taking part at various levels in the individual patient-doctor interaction, as well as in the overall safety net for drugs.

The 2 main professions that are also involved in pharmacovigilance are clinical pharmacists and clinical specialists.

Clinical pharmacists are highly competent in their field and are very much involved in pharmacovigilance and drug safety in many countries. They play an important role in the prevention of ADRs, as has been shown in anticoagulant clinics or in drug–dosage adjustment. However, despite their name, they are not clinicians and have no clinical experience in the sense of dealing directly with patients in the diagnosis and global management of disease. If it comes to discussing an individual patient with the treating physician, looking at alternatives to the causal drug hypothesis and the overall patient management, the pharmacist lacks the necessary specific clinical expertise. On the other hand, because of their training, clinical pharmacists are invaluable in a regional centre team and as a relay in hospital wards between the clinicians and the clinical pharmacologist and pharmacovigilance centre. However, they must be included in the team with clinicians. This is in fact the usual setup in French Regional Centres, where the director of the centre must always be a clinical pharmacologist, i.e. a physician.[23]

Clinical specialists are also vastly knowledgeable in their field of specialty. They are invaluable expert knowledge resources and can participate in centre activity in matters related to their clinical fields. Tight focusing in a specific specialty, however, limits their capability to interact in the very diverse fields involved in daily pharmacovigilance, and most do not have the necessary background training in general pharmacology – otherwise they are *de facto* clinical pharmacologists.

7. Conclusions

Managing ADRs should be a natural activity for clinical pharmacologists. This management takes advantage of all the skills of a clinical pharmacologist in pharmacology and in clinical practice, their understanding of pharmacoepidemiology and knowledge of the availability of pharmacokinetic and fundamental research labs, to explore individual cases and the mechanisms of ADRs. Specialisation in drug-induced diseases is a highly complex and multifactorial discipline. This provides an opportunity for the recognition of the unique role of the clinical pharmacologist in hospitals. This is a rather exciting perspective for a discipline that sometimes seems to wonder what its future is.

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References

1. Dormann H, Muth-Selbach U, Krebs S, et al. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. Drug Saf 2000; 22 (2): 161-8
2. Moore N, Lecointre D, Noblet C, et al. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol 1998; 45 (3): 301-8
3. Tramer MR, Moore RA, Reynolds DJ, et al. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000; 85 (1-2): 169-82
4. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. Pharmacoeconomics 1999; 15 (5): 445-58
5. Rawlins MD. Clinical pharmacology. Adverse reactions to drugs. BMJ 1981; 282 (6268): 974-6
6. Rawlins MD. Spontaneous reporting of adverse drug reactions. I: the data. Br J Clin Pharmacol 1988; 26 (1): 1-5
7. Rawlins MD. Spontaneous reporting of adverse drug reactions. II: uses. Br J Clin Pharmacol 1988; 26 (1): 7-11
8. Pouyanne P, Haramburu F, Imbs JL, et al. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. French Pharmacovigilance Centres. BMJ 2000; 320 (7241): 1036
9. Imbs JL, Pouyanne P, Haramburu F, et al. Iatrogenic medication: estimation of its prevalence in French public hospitals. Regional Centers of Pharmacovigilance. Therapie 1999; 54 (1): 21-7
10. Salom IL, Davis K. Prescribing for older patients: how to avoid toxic drug reactions. Geriatrics 1995; 50 (10): 37-40
11. Dartnell JG, Anderson RP, Chohan V, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. Med J Aust 1996; 164 (11): 659-62
12. Moore N, Verschuren X, Montout C, et al. Excess costs related to non-steroidal anti-inflammatory drug utilization in general practice. Therapie 2000; 55 (1): 133-6
13. Capella D, Laporte JR, Vidal X, et al. European network for the case-population surveillance of rare diseases (Euronet). A prospective feasibility study. Eur J Clin Pharmacol 1998; 53 (5): 299-302
14. CAST investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N Engl J Med 1989; 321 (6): 406-12
15. Council for International Organizations of Medical Sciences. Benefit-risk balance for marketed drugs. Calculating safety signals. Geneva: CIOMS, 1998
16. Wang RI. The definition and scope of clinical pharmacology. JAMA 1980; 243 (19): 1901-2
17. Backstrom M, Dahlqvist R, Mjorndal T, et al. A regional center for reporting adverse drug reactions in Umea. Prompt handling results in quick feedback. Lakartidningen 1995; 92 (3): 148-50
18. Blayac JP, Haramburu F, Lerebours S, et al. Drug information and prescription guidance: role of regional centers of pharmacovigilance. Presse Med 2000; 29 (2): 115-8
19. Mariani L. Pharmacovigilance: education and continuing updating. The role of university institutes. Clin Ter 1998; 149 (3): 219-25
20. Schwarz UI, Stoelben S, Ebert U, et al. Regional drug information service. Int J Clin Pharmacol Ther 1999; 37 (6): 263-8
21. Troger U, Meyer FP. The regional drug-therapy consultation service centre – a conception that has been serving patients and physicians alike for 30 years in Magdeburg (Germany). Eur J Clin Pharmacol 2000; 55 (10): 707-11
22. Hoffmann A, Hippius M, Sicker T. Adverse drug reaction monitoring in Jena--experiences of a regionalized pharmacovigilance centre. Exp Toxicol Pathol 1998; 50: 453-7
23. Moore N, Biour M, Paux G, et al. Adverse drug reaction monitoring: doing it the French way. Lancet 1985; II (8463): 1056-8
24. Laporte JR, Capella D. The Spanish drug surveillance system. Med Clin (Barc) 1994; 103 (9): 335-6
25. Wiholm BE, Olsson S, Moore N, et al. Spontaneous reporting systems outside the United States. In: Strom B, editor. Pharmacoepidemiology. 3rd ed. Chichester: John Wiley & Sons, 2000: 139-155

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