Clinical pharmacology in Serbia: the time for new challenges

Klinička farmakologija u Srbiji: vreme novih izazova

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Introduction

During the recent 4th European Summer School in Clinical Pharmacology and Therapeutics in Vršac (2006, September 16–20), organized by the European Association of Clinical Pharmacology and Therapeutics (EACPT) and the Clinical Pharmacology Section (CPS) of the Serbian Pharmacological Society (SPS), as well as the International Federation of Associations of Pharmaceutical Physicians and the Serbian Association of Pharmaceutical Physicians it was obvious that the status of clinical pharmacology still varies widely from country to country in Europe 1, 2. Namely, in spite of many initiatives, its development in many countries is too slow. The aim of this review was to present the development and the state of the art of clinical pharmacology in Serbia.

The historical background of the discipline

Clinical pharmacology originates from the development of methods for formal testing of new medicines in men – especially from the randomized, controlled clinical trials. In 1932 Paul Martini published a monograph entitled "Methodology of Therapeutic Investigation", that summarized his experience in scientific drug evaluation and, probably after which he was named the "first clinical pharmacologist" 3. Although the resources, as well as expertise needed to develop new drugs were primarily concentrated in pharmaceutical industry, especially in the USA, academic clinical pharmacologists, like Harry Gold and Walter Modell, also in 1930s, made important contributions to the design of clinical trials 4. Yet, it was not until 1952 that Harry Gold, who was considered to be the founder of the modern discipline of clinical pharmacology, first formulated the need for the establishment of a separate discipline incorporating basic pharmacology and clinical medicine, for which special kind of investigators were needed 5. Clinical pharmacology was actually born as a result of the explosion of new and highly active therapeutic drugs that were discovered between early 1950s and 60s. The concept of randomized, controlled clinical trial, as the principal methodological tool, was defined as any carefully planned, ethically acceptable experiment on man, designed to answer a clearly defined question 6, 7. Several drug disasters, like thalidomide one, further urgented the medical need to commensurate, in scientific terms, the benefits of drug therapy relative to its risks 8–10.

The World Health Organisation (WHO) study group reviewed the broad scope of activities of clinical pharmacology, so in 1970 it became an established medical discipline in a number of countries, especially the Nordic ones (Denmark, Norway and Sweden), the United Kingdom and the United States 11. They pointed out the need for integrating clinical pharmacology into the health service system and making its services available according to the local conditions. However, although individuals trained in clinical pharmacology in the US were highly competent professionals, most of them worked in pharmaceutical industry, academies and governmental agencies, but none in the national health care system, and, on the whole, their number was rather small 12, 13. Recently, in the report of the American Board of Clinical Pharmacology, as an independent accrediting body, it has been shown, for example, that from 1991 to
1999 only 260 individuals were certified and accredited as either clinical or applied pharmacologists 14, most of them being medical doctors, but also pharmacists or those who have PhD degree in biological sciences. Luckily, the situation in Europe used to be different from the beginning, focusing both on research and well-defined health care services 15, 16. One of the founder of the discipline in Europe, Professor Folke Sjöqvist said: “In order to function well, a clinical pharmacologist needs to be needed. He must, therefore, provide skills and know-how about drugs that other members of medical profession lack or cannot easily mobilize”. In order to achieve these goals, in 1986 WHO Working Group on Clinical Pharmacology in Europe again set general principles, not only for teaching clinical pharmacology, but also formulated guidelines on the role of the discipline in health care delivery 17, 18.

The Serbian beginnings

The development of this discipline varied widely across the Continent. Former Yugoslavia used to consist of six republics and two autonomous provinces, each being responsible for its own health affairs. As a result of this, there existed various development patterns of the discipline 19. In Croatia, for example, clinical pharmacology developed from the internal medicine, as an university department in Zagreb and an unit in Split, had clinical responsibilities for inpatients and outpatients facilities. In other republics, including Serbia, it developed from basic pharmacology. One of the pioneers of clinical pharmacology in former Yugoslavia, Professor Božidar Vrhovac (University Hospital, Zagreb), in the very same year when the mentioned WHO report of the experts appeared 21, informed medical public about the roles and tasks of this medical discipline 26. According to him, implementation of pharmacologic principles should benefit patients, decrease their exposition to potentially dangerous medicines and, through the teaching of modern principles of pharmacotherapy, promote the scientific application of medicines.

Soon after that in 1974, it became a recognized medical specialty in Croatia 21. The need for the introduction of clinical pharmacology as an official medical speciality was also fully present in Serbia 22-24. Some of the leading basic pharmacologists in Serbia, like Professor Vladimir Varagić (Medical Faculty, Belgrade), late Professors Miloš Medaković and Branko Banić (Medical Faculty, Novi Sad) 22-24 and Professor Bogdan Bošković (Military Medical Academy, Belgrade) 29-32, clinically trained professionals as late Professor Dragan Simić, internist (Clinical Hospital Centre „Dr Dragiša Mišović”) 33-35 and Professor Milan Stanulović 32, trained in biochemistry (1962–1968) and paediatrics (1968-1974) became involved in the development of this discipline. Concerning the Military Medical Academy, a great contribution to the clinical pharmacology was given by Professors of internal medicine Ratibor Mićić, Slavko Krstić and Milan Popović, as well as colonel Svetomir Bećanović, MD. This enabled further development of clinical pharmacology, not only in the Military Medical Academy, but through their engagement in various federal drug commissions, to its development in Serbia, as well.

The scientific and educational board of the Medical Faculty in Novi Sad and its Department of Pharmacology and Toxicology formally introduced the clinical pharmacology as postgraduate programme (MSc, and PhD degree) in 1975 22. Besides the youngest members of the Department, these studies were successfully completed by many doctors from the clinics or those employed in pharmaceutical industry. However, first formally trained clinical pharmacologist in Serbia was Prof. Milan Stanulović, who after his stays in Great Britain, Nordic countries and the United States, passed his examination at the Board of Croatia in Zagreb, in 1984.

An independent medical residency programme of clinical pharmacology was established on the 22nd of August 1981 at the Medical Faculty in Belgrade 36. A 3-year training of the graduated as MDs, consisted of 13 months spent at the Institute for Basic Pharmacology, 9 months of formal lectures and 14 months of clinical training. A shorter training programme, clinical pharmacology subspecialty, lasting 18 months, also existed for specialists in internal medicine, anaesthesiology, general surgery, paediatrics, infectious diseases and neuropsychiatry.

Although the formal prerequisite had existed for many years, the role of clinical pharmacology, as a whole, and especially in health care delivery was far from prominent for a long time. As already stated, it was developed from basic pharmacology in Serbia, and this fact influenced greatly the development and professional activities of clinical pharmacologists. In the beginning, most of the specialists were employed at the institutes of basic pharmacology, as well as in industry, often without the real connections with everyday clinical practice. On the other hand, most of the sub-specialists have continued to perform their basic professional activities after completing formal education, without too many opportunities to apply new theoretical and practical skills. Therefore, clinical pharmacology survived for a long time owing to enthusiastic work of groups or committed individuals who believed that it was worth fighting. For example, drug utilisation and pharmacoepidemiology were introduced to the Institute for Pharmacology, Toxicology and Clinical Pharmacology, Medical Faculty, Novi Sad, and these studies were among the first pharmacoepidemiological ones at the territory of former Yugoslavia 37, 38, although there were also successfully planned and performed ones in the other university centers 40. Activities and publications in the field of the paediatric clinical pharmacology, which some of the members of the institute have performed, were also pioneering ones both in the country, and abroad 31, 42.

The main activities

During the early days, the main tasks of clinical pharmacologists in Serbia were clinical trials, drugs committees (DC), adverse drug reactions monitoring, pharmacotherapeutic information services and teaching and education in the discipline.

Clinical pharmacologists participated in planning and conductioning the controlled clinical trials, in collaboration with clinicians. Military Medical Academy, for example, was entitled by the Republic Secretariat of Health and Social Welfare to carry out clinical trials since 1973 and all of its 4 clinical pharmacologists and one clinical pharmacist were included in them in a ceratin way 45–46. Through their activities in planning and organization of pharmacokinetic bioequivalence studies and development of new analytical methods the Institute for Pharmacology, Toxicology and Clinical Pharmacology at Medical Faculty in Novi Sad 57, 42, National Poison Control Centre, Military Medical Academy in Belgrade 49, 50 and Department of Pharmacokinetics at the Faculty of Pharmacy in Belgrade 51, 52 contributed to the development of new generic products and gave new theoretical solutions in pharmacokinetics.

The tradition of the DC in Serbia goes back to early eighties of the previous century 24. In the Military Medical Academy, DC was founded on the 11 January 1980 and Professor Bogdan Bošković, a pharmacologist and toxicologist, was the first one who chaired it. It had 14 members. At the Medical Faculty in Novi Sad it existed since September 1982. It had 17 members and its first president was Professor Milan Stanulović, pharmacologist and paediatrician. It actually derived from the Committee for Pharmacotherapeutic Formulary, founded in December 1977. Their tasks were, and still are, the evaluation of applications for the controlled clinical studies in hospitals, as well as their surveillance until the end, reporting adverse drug reactions, discussing drug utilisation, defining hospital formularies, adopting clinical guidelines and other activities through which clinical pharmacologists may influence rational drug prescribing in a hospital.

Reporting adverse drug reactions is also one of the main activities of clinical pharmacologists, and the Institute for Pharmacology, Toxicology and Clinical Pharmacology in Novi Sad was one of the most active Regional Centres in Serbia 53. On the other hand, the National Center for Adverse Drug Reactions Monitoring (NCADRM), founded in 1994 in Clinical Centre of Serbia, enabled all general conditions necessary to apply the WHO Programme for adverse drug reactions monitoring 54. In the year 2000, it became a full member of the WHO Uppsala Monitoring Centre (UMC). The major tasks of NCADRM were detecting adverse drug reactions and reporting them to all health care professionals, as well as sending to UMC, especially those that were presented as serious adverse reactions to drugs. There were also some very good publications concerning adverse drugs reactions which were valuable for clinical pharmacologists as well as for other medical doctors and pharmacists interested in the field of pharmacotherapy 55–58.

Giving drug information to colleagues and other medical staff, as well as to patients, is also one of the very important tasks of clinical pharmacologists which can be fulfilled in various ways. For example, the Institute for Pharmacology, Toxicology and Clinical Pharmacology in Novi Sad has been publishing periodic publications „Drugs at the Market“ from 1992, and it has entirely been transferred to electronic discs enabling efficient PC research 59, 60. This also helped the members of the institute very much to give the required information concerning drugs by the telephone to anyone interested in, from the country, or abroad 24. Prof. Bogdan Bošković, from the Military Medical Academy, used to write and publish a periodic publication „News in Pharmacotherapy” from 1980 to 2002 which offered the author’s review of the most interesting and most important articles concerning different fields of pharmacotherapy from the most cited medical journals, for the year. There are also available some other valuable publications concerning the same issue in our country 61–63, among which a monthly published „Pharmacotherapy today” edited by Ankica Jelenković, MD, PhD, a specialist of clinical pharmacology, deserves a special attention.

Teaching of clinical pharmacology in Serbia, as above mentioned, started in 1975 in Novi Sad, as postgraduate programme (MSc and PhD degree) 25 as well as in 1981 in Belgrade, when it became an independent medical residency programme 58 resulting from understanding that it is the necessity and one of the three main roles of this medical discipline 18, 22, 64–66. Thanks to the efforts and enthusiasm of professors Vladislav Varagić, Tomislav Kažić, Leposava Grbović, Ranka Samardžić and Milica Prostran, who led the postgraduate studies in clinical pharmacology at the Institute for Pharmacology, Clinical Pharmacology and Toxicology at the Medical faculty in Belgrade, as well as Professors Milan Stanulović, Ana Sabo and Momir Miko in the Institute for Pharmacology, Toxicology and Clinical Pharmacology at Medical Faculty in Novi Sad, 90 clinical pharmacology specialists and subspecialists completed their professional education until 2005 67, 68.

The main challenge – recognition of clinical pharmacology by National Health Service

Some of the leading members of the CPS of the SPS also contributed to the development of clinical pharmacology in Serbia. The section was founded in 1994 and here are some historical milestones of it: Professor Tomislav Kažić (President) and Professor Siniša Radulović (Secretary) acted from 1994–1998 69, Professor Milan Stanulović (President) and Associate Professor Miloš P. Stojiljković (Secretary) from 2003 and Associate Professor Miloš P. Stojiljković (President) and Assistant Professor Viktorija Dragović-Simić (Secretary) from 2003–2007, also as Acting President from 2004–2006.

In spite of all, however, the development of this medical discipline have been too slow so far and, from the very beginning, there have been difficulties in defining its performance targets within the National Health Service (NHS). Therefore, the current Presidency of the CPS of the SPS launched the project of improving the status of clinical pharmacology in our country and the first created, detailed register of all clinical pharmacologists educated in Serbia and/or have been working in our country since 1981 68.

Then, the role and impact of clinical pharmacologists on health care in Serbia was investigated in two ways: by field survey and by a questionnaire. The results have shown
that 50% of the responders (60 clinical pharmacologists) worked in the NHS and that the scope and quality of health care services given by clinical pharmacologists were the best in the tertiary health care hospitals with the independent departments of clinical pharmacology. The tradition of the existence of the unit of clinical pharmacology, as well as the efforts of establishing it in hospitals is very long at the territory of former Yugoslavia.

This complies with the previously mentioned recommendations of WHO according to which all the functions of clinical pharmacologists, such as clinical pharmacology service, training in clinical pharmacology and clinical pharmacology research should be done at the hospital. For this reason the Technical Report ofWHO clearly states that „hospital beds and outpatient facilities must be available for clinical studies, and clinical pharmacist should be fully responsible for his patients“. However, other authors have considered that every clinical pharmacist simply cannot perform all the suggested functions, especially if he/she has direct clinical responsibilities, and clinical pharmacologists who cannot get their message to their colleagues in other disciplines will not be helped simply by running their own word and particularly by practising general medicine. However, everybody agree that in case of no separate department or unit available, it is the minimum requirement that the specialist of this discipline has access to a patient and is actively involved in patient care. One of the suggestions of our prominent clinical pharmacologists, more than 20 years ago, was the model of the unit in large university hospital with 10–20 patient beds, two to four responsible specialists, one to three residents and several nurses specially trained for organization of clinical trials, involvement in surveillance of adverse drug reactions, drug consumption etc. Beside the small ward, unit should also have its office, small laboratory, as well as outpatient room. Therefore, the departments may have been established either as separate units, or within existing departments of pharmacology or internal medicine. In Sweden, for example, a hospital provides staff for the clinical pharmacology services, while medical school provides position for research and teaching. Therefore, it is not generally defined how such facilities should be organized, and national and local circumstances have to be considered.

There are three academic departments in Serbia at the moment: at the Medical Faculty in Belgrade, Novi Sad and Kragujevac, all as joint departments with pharmacology and toxicology. However, the first clinical pharmacology unit inside a hospital, which was founded in 1989 and still fully operational, was situated in the Institute for Oncology and Radiology of Serbia. Although long time has passed before the other ones have been formed awareness that improvement of patient care by promoting the safer and more effective use of drugs can not be exercised without an effective service organization was permanently present. However, during the last 10 years several clinical pharmacology services were formed, all inside the tertiary health care hospitals and as independent units: the Center for Clinical Pharmacology in the Clinical Center of Kragujevac (since 1995) and in the Clinical Center of Serbia (since 2003), the Center for Pharmacotherapy in the Clinical Center of Niš (since 2004) and Centre for Clinical Pharmacology in Military Medical Academy (since 2005).

Presence and future

Both above mentioned field survey and the questionnaire indicated that the following services were most often provided by clinical pharmacologists in the Serbian health care system by giving drug information, drug utilization analyses, taking part in the work of DC and ethics committee, drug/patient problem consultations, hospital’s drug formulary, auditing of prescribing practice, taking part in drug clinical studies, continuing medical education, predispensing control of prescribing and therapeutic drug monitoring, as well as by drug supplying and procurement management. The broadest spectrum of services was given by clinical pharmacologists from the Center for Clinical Pharmacology at the Clinical Centre of Kragujevac. Therefore, our clinical pharmacologists are becoming more and more indispensable to hospital managers and clinicians, but this is possible only through their everyday involvement in clinical practice, as shown by the experience of the others. In May 2006 two regulations on organization of health care facilities in our country were issued by our Ministry of Health. Due to better understanding of the current role of clinical pharmacology in the country, the introduction of independent CP service in tertiary and secondary health care hospitals is foreseen, and, according to these regulations, one specialist of clinical pharmacology per 400 patient beds should perform his/her professional activities, while in the clinical centers their number should be 1.25 per 400 patient beds.

We are convinced that the introduction of clinical pharmacology into general district hospitals and enabling our specialists to have service role in all mentioned areas, both in secondary and tertiary health care facilities, will not only ensure further development of the discipline itself, but will also contribute to the better health care system, as a whole. We not only consider clinical pharmacology “too young to die”, on the contrary, agree but that the future of it, as seamless continuation of basic one ought to be bright and, the sooner we get this work done, the sooner we can see the bright light at the end of the „tunnel“ in which clinical pharmacology has been for years in our country.

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