WHO Drug Information

Contents

Personal Perspectives

Unfinished business: clinical pharmacology and world health 201

Safety and Efficacy Issues

Transdermal fentanyl: abuse by adolescents 207
Safety of fentanyl transdermal patches 207
Rosiglitazone: decreased high-density lipoprotein cholesterol 208
Ibuprofen: Stevens-Johnson syndrome 208
Stringent conditions for COX-2 inhibitors 209
Sildenafil, tadalafil and vardenafil: eye problems reported 209
Nesiritide: safety report and measures 210
Mifepristone, sepsis and blood infection 211
Mifepristone: revised safety information 211
Suicidality with SSRIs in adults 211
Ezetimibe and muscle disorders 212
Pathological gambling with cabergoline 212
Icodextrin peritoneal dialysis solution: falsely elevated blood glucose readings 213
New requirements for pseudoephedrine products 213
Efalizumab: warning of thrombocytopenia 214
Antiretrovirals: HIV, hepatic impairment and HBV/HCV 214

Herbal Medicines

Monograph for cultivation of herbal antimalarial: *Artemisia annua* 215
Ayurvedic medicines and heavy metals 215
National policy on regulation of herbal medicines 216
Regulatory guidelines for complementary medicines 216

Regulatory Action and News

Hydromorphone extended release suspended 217
New drug safety initiative 217
Deregistration of thioridazine 217
Caution on self medication 218
European marketing authorizations 218
Tigecycline: first-in-class antibiotic approved 219

Essential Medicines

Highlights of the 14th Model List of Essential Medicines 220
Methadone and buprenorphine 220
Mifepristone with misoprostol 220
WHO Model List of Essential Medicines 222

Access to Medicines

Intellectual property protection: impact on public health 236

The International Pharmacopoeia

International Pharmacopoeia: fourth edition in development 242

Recommended International Nonproprietary Names: List 54 243

Personal Perspectives

Unfinished business: clinical pharmacology and world health

Clinical pharmacology has existed for just over 40 years and is a relative newcomer to the range of clinical specialties. It took its origins from the development of methods for the formal testing of new medicines in man – especially the randomized, controlled, clinical trial – and from the major concerns about safety of medicines catalysed particularly by the thalidomide disaster of the early 1960s [9]. Essentially, it is the scientific study of medicines in man and has developed its own methodological approaches ranging from single dose studies of medicines in individuals and small groups to wider studies of medicines use in whole populations. Among several enabling branches of the discipline are pharmacovigilance (the monitoring and study of the safety of medicines), pharmacokinetics, drug metabolism, pharmacoepidemiology and more recently, pharmacoeconomics. Many collaborative partnerships have been forged with pharmacists, analytical chemists, statisticians, other clinicians and, more recently, epidemiologists and health economists, in developing these themes.

As a new discipline clinical pharmacology has had to fight for recognition, both in medical schools but also in the wider world of health care delivery. This is perhaps surprising when one of the main tasks of any physician is the safe and effective prescription of medicines, and of any health service to ensure the availability of medicines of high quality, safety and efficacy to be used in the most cost-effective manner. (Costs of medicines may be 10% of total healthcare spending in the public system in developed countries but for many developing countries often exceed 30% of health budget.) However, the demand for a new lecturer in molecular biology in a medical school, a new cardiologist in a teaching hospital or a further administrator in a health service commonly takes precedence over creating a position for a clinical pharmacologist.

If clinical pharmacology has had some difficulties in making its presence felt in the developed world, these have been much greater in developing world countries where medical needs are often comparatively much greater but available, trained personnel are few.

Against this background, recently revised "Aims and Functions of the International Union of Basic and Clinical Pharmacology (2) include . . . "helping in all ways the development of pharmacology throughout the world particularly in emerging countries". The aims include "(to) improve and harmonize the teaching of rational use of drugs . . . particularly in developing countries" and "(to) improve the utilization of clinical pharmacological services in health care delivery, particularly in developing countries. . ."

Developing–developed world collaboration in clinical pharmacology

Distance and the lack of easy communication militated against collaborative work between developed and developing countries for many years. An exception was the work of D.R. Laurence, a pioneer clinical pharmacologist from the United Kingdom who worked over several years with colleagues from Bombay (now Mumbai), India to determine the safe and effective dose of tetanus antitoxin for the treatment of this (now largely preventable) disease. Their conclusions in 1968 were that "in the treatment of tetanus 10 000 IU (international units) of equine antitoxin is about as effective as 200 000 IU" [14].

Remarkably, this was the first systematic attempt to define a rational dose of antitoxin but it also established that inter-country collaborations on

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Article adapted from the IUPHAR Clinical Pharmacology lecture of the same title given at the 8th World Congress of Clinical Pharmacology and Therapeutics, Brisbane, Australia, August 2004. It appeared in: International Journal of Risk & Safety in Medicine, ***17****: 65–71 (2005) authored by Anthony J. Smith, Department of Clinical Pharmacology, University of Newcastle and WHO Collaborating Centre for Training in Pharmaco-economics and Rational Pharmacotherapy, Australia.*

matters of importance to public health were possible and could yield answers which reduced the cost of provision of services in the public sector, in this case by a factor of 20.

In the late 1960s and throughout the 1970s a trickle of young trainees from developing countries was funded to work in clinical pharmacology units in Europe and the USA. In retrospect, the unawareness of many of the host departments of the needs of the developing country, and the immaturity of the discipline itself often meant that their training was not tailored to real needs. For instance, acquiring skills in the measurement of small amounts of medicines in blood samples was not relevant for a trainee going back to a country which had difficulty in providing even essential medicines to the poorest of its people let alone setting up a sophisticated analytical facility in which the trainee could practice his new-found techniques. This lack of congruence between training and career prospects often led to disillusion and migration of the trainee either back to the laboratories of the developed world or into a different clinical specialty at home.

The advent of the Internet coupled with easier travel has transformed the possibilities for collaboration between developed and developing countries and there are many examples of partnerships producing important research findings of direct benefit to both partners. Malaria remains one of the most perplexing tropical diseases and the long-standing collaboration between Oxford University and the research group in Mahidol University in Thailand is a good example of a better approach to research into issues of safe and effective treatment [16]. A simple but relevant study of the efficacy and safety of rectal artesunate compared with quinine in the same disease published in 2004 was conducted by a team including clinical pharmacologists from both developed and developing African countries [3]. Increasingly, research collaboration is occurring between African and Asian centres and clinical pharmacologists in developed countries, particularly relating to malaria but also to other tropical diseases.

The benefits of collaboration are by no means one-way and the placebo-controlled trial finally confirming the value of magnesium sulphate treatment in pre-eclampsia could only have recruited its 10 000 patients over a short time period by working collaboratively with clinicians and clinical pharmacologists in several developing countries. The results are applicable to both developed and developing communities [1].

Clinical toxicology has often been a neglected area of research. Here again recent inter-country collaborations have advanced knowledge – for example, the Oxford–Colombo research unit working on the management of poisoning both with organophosphate insecticides (estimated to kill 200 000 people worldwide each year) and with Oleander species – plants often taken with suicidal intent in Sri Lanka and containing glycosides with a digoxin-like cardiotoxic effect which, untreated, may be rapidly fatal [7].

Recently several centres of clinical pharmacology have developed collaborative programs concentrating on training in rational medicines use. Examples include the current Egypt–Denmark–Sweden collaboration on rational prescribing and Spanish initiatives linking clinical pharmacology training into the health care systems of Central and South American countries.

Applying research lessons to the use of medicines in the health care system

Are the newly-won lessons coming from the developed-developing research partnerships having an impact on health services? The evidence obtained is “necessary but not sufficient” to ensure its translation into health policy and delivery of health care but there are pointers to ways in which this might be done.

Experience gained in Australia over the past 13 years shows that the role of the clinical pharmacologist can be a central one in helping translate the scientific evidence into health care practice. The new feature that has brought these together is the creation and implementation of a National Medicines Policy (NMP) based on the prototype of the World Health Organization (WHO) [19]. Many of the ingredients of a NMP have existed in Australia for many years. Quality, safety and efficacy of new medicines are regulated by the Therapeutic Goods Administration while equity of access to medicines is assured by the subsidies provided by central government and administered by the Pharmaceutical Benefits Scheme. Both of these have been in place for over 50 years. However, after much lobbying, particularly by consumer organisations and in line with WHO guidelines, Quality Use of

Medicines was adopted by government as an additional component of the policy in the early 1990s.

The committee appointed to have oversight of this new policy direction conducted research into local and overseas practice, sponsored new investigation and tested interventions where necessary. By 1995, it was in a position to collate the evidence about improving the quality of use of medicines into a document suitable as a blueprint for intervention on a national scale. In 1997, the, then, Minister for Health announced funding for a National Prescribing Service (NPS) to implement these strategies and evaluate their impact. The NPS was set up as an independent company receiving its funds from government but independent from it in all other respects. It has implemented many interventions over the past 6 years with evidence of benefit in terms of the more rational use of medicines – especially antibiotics [15]. Within this national enterprise most of the country's clinical pharmacologists (almost all of them on the staff of University Medical Schools) have found important and relevant roles. In this, the translation of research findings into the delivery of health care services can be clearly seen and the role of the clinical pharmacologist defined. The Australian NMP was revised and published in its present form in 2000 [2].

Advocacy at a political level

Most health departments in developing countries have little or no contact with clinical pharmacology and rely very heavily for advice about pharmaceuticals on pharmacists who have worked in the bureaucracy often for many years. Many have given great service but few have a clinical dimension to their experience and therefore are often unaware of emerging research evidence about medicines and commonly are not in constant touch with practitioners working in the hospital or community. A clinical pharmacologist can provide the link between government and the health care community and can also be a powerful advocate for the introduction of new services (e.g., the systematic collection of data about adverse reactions to medicines or the strengthening of prescribing education in a medical school curriculum). Politicians without a health training are not aware of the distinctive role that clinical pharmacology can have and fail to recognize the discipline as separate from "pharmacology" or "pharmacy".

Lack of recognition means clinical pharmacologists commonly are not regarded as full specialists. This, in turn, carries the implication of poorer overall salaries, often no right of private practice and a poorly formulated job description. Recruitment into clinical pharmacology is adversely affected by this, and young people who might contribute to the overall goal of improving drug use understandably opt for the safer clinical specialties. There is an urgent need for advocacy at government level to redress these perceptions and demonstrate the value of clinical pharmacology to any health care system.

Development of national medicines policies

A national policy provides a blueprint for the future, can be divided into discrete areas which can be allocated to the most appropriate groups to implement and also stands as a document against which progress can be measured. Governments change and new ones may sometimes abolish policies made by their predecessors. This is unlikely to happen if the policy commands general support within the health care professions and, especially, from consumers. Ideally a policy should be developed with input from all those with a stake in it. This implies inclusion of members of the government and its officers, health professionals including pharmacists, nurses, clinical pharmacologists and other and medical practitioners and, wherever possible, representatives of consumer organizations. A well supported and agreed policy will have fewer problems in its implementation stage.

Implementing policy

There are many tasks under this one heading. Among them are compiling evidence-based essential medicine lists and standard treatment guidelines and providing objective, relevant medicines information as most health professionals in developing countries rely almost entirely on the pharmaceutical industry for their information.

Perhaps one of the most relevant tasks in the present climate of heightened concern about safe use of medicines is the development of systems for the detection and monitoring of adverse reactions and of a process that can respond to these in a timely manner. [Some developing countries have an extra concern about medicines available to consumers as up to 25% may be counterfeit, containing none of the active product, or at best a reduced amount [20]. While not technically recognized as such, failure to improve

due to lack of the expected ingredients in a medicine might well be classified as an adverse response.]

However, even a fully developed monitoring system will not detect all the safety issues relating to prescribed medicines and formal studies are often required. As an example, a detailed study of safety in Australian hospitals [17] published in 1995 found that 16.6% of hospital patients, in a random survey of 14 179, had some form of adverse event. Of these almost 11% were related to medication. Further analysis showed that the elderly were most at risk, poor prescribing practice contributed and that failure to monitor the consequences of medicines administration was the commonest direct cause of the adverse event. More than 80% of the adverse events were judged to be preventable [4]. A later overview of 14 published Australian studies [11] confirmed that between 2.4 and 3.6% of all hospital admissions were reported to be medicine-related with the highest proportion (15–22%) in the elderly. Thus, we have sufficient evidence about incidence and factors influencing adverse response to provide a basis for intervention – currently being undertaken at a national level by, among others, the Australian Council for Safety and Quality in Health Care [12].

While WHO has recently identified patient safety as a global priority and in 2004 launched the Word Alliance for Patient Safety [6], there are many developing countries in which fundamental data gathering, let alone formal studies, for the detection of adverse response to medicines is yet to be established. The WHO Collaborating Centre in Uppsala, which carries the responsibility for International Drug Monitoring, receives data about adverse response to medicines from only 73 countries (annual report 2003–2004 [13]) with a further 13 currently trying to develop their data systems to the point of compatibility with the Centre's requirements. As more than 150 countries worldwide now have national medicines policies it appears that the safety aspect of these policies has not yet received the priority it deserves.

Paradoxically, it can be predicted that for many developing countries there is some safety protection in relying on an Essential Medicines List for supply of medicines as these lists commonly contain older, better known medicines whose adverse effect profile is well established. There is therefore the small consolation of less concern about newer medicines whose safety has become a concern only after wider use in developed countries and which have subsequently been withdrawn from the market.

The clinical pharmacologist should also have a role in the development and implementation of drug regulatory systems, and (particularly, but not exclusively, in poorer countries) for the cost-effective purchase of medicines, as the comparative performance of medicines in clinical use is the basis for deciding which is the most cost-effective and therefore most suitable for inclusion in a national formulary or a list of subsidised medicines.

For many developing countries herbal and other complementary medicines are first-line medications. For many of these the evidence of safety and efficacy falls below the standards that would be expected of prescription medicines. This is an important area for local research which must include relevant clinical trials.

Finally, but probably as important as any other aspect of national policy, is the centrality of good education about prescribing. An average prescriber writes over 250 000 prescriptions in a practising lifetime – some write many more – yet the quality of prescribing leaves much to be desired in both developed and developing countries. For many medical schools pharmacology and even clinical pharmacology teaching are well established but the extra step which translates theoretical knowledge into the practical skills of prescribing does not feature in the curriculum and graduates are left to "pick up" prescribing once they are exposed to the realities of everyday practice. There is now a well evaluated WHO programme [5,18] which adopts a problem-based approach to selection of medicines for prescription and encourages the student to build a personal, evidence-based formulary. Teachers have found it valuable and young graduates who have been through the course have a much greater confidence in their abilities both to prescribe and to maintain their formulary current as new medicines are introduced or older ones removed. In Australia the course has been adapted for computer-interactive learning and is being used in most medical schools [10].

Thanks to work conducted by many concerned people in both developed and developing countries there is now an adequate body of evidence about interventions that work (and those that do not) to enable any country to improve the use of

medicines. An article outlining these interventions states “Sufficient evidence is now available to persuade policy makers that it is possible to promote rational drug use. If such effective strategies are followed the quality of health care can be improved and drug expenditure reduced” [8].

Implications for the developing world: training and employment of clinical pharmacologists

The list of tasks generated around a national medicines policy gives an idea of the newer roles being taken on by clinical pharmacologists, often working from an academic base, as key members of the teams required to put in place strategies to improve the quality of use of medicines. However, the list also suggests the training and skills base required by any clinical pharmacologist who becomes involved in this process. The newer roles do not make conventional postgraduate training in the discipline irrelevant but additional skills and knowledge are needed for the new tasks.

Some clinical pharmacology departments do have sufficient involvement in national policies to be able to provide the necessary hands-on practical training but too many do not. If the supplementary training is to be made available there is need for a focus on both recruitment of trainees and provision of suitable training.

This seems to be an ideal opportunity for an alliance between IUPHAR (and particularly its Clinical Pharmacology Division, with its stated aims of improving the reach of the discipline into health care delivery) and WHO with its concerns for the appropriate, safe and effective use of high quality medicines in all countries, and not solely in the richer parts of the world. Out of such an alliance might emerge a new training programme, perhaps a “fellowship” scheme for trainees, with guarantees from their home governments of a career path at completion of training. Some ongoing links between the trainees and their mentors would be appropriate and the training itself could be carried out both in the home country and, for part of the time where needed, in an overseas training institution. With the increasing use of computer-based instruction and interaction the previous problems with communication should be easily overcome. Donor support would be needed. There are some donors for whom this sort of program would be attractive and consistent with other areas related to rational use of medicines which they have already supported. In this way it might be possible to harness the potential for clinical pharmacology to make its full, and currently under-exploited contribution to the improvement of world health.

References (alphabetical)

[1] D. Altman, G. Carroli, L. Duley, B. Farrell, J. Moodley, J. Neilson and D. Smith. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial, *Lancet* **359** (2002), 1877–1990.

[2] Australian Government. Department of Health and Ageing. National Medicines Policy (2000), http://www.nmp.health.gov.au/pdf/nmp2000.pdf.

[3] K.I. Barnes, J. Mwenechanya, M. Tembo, H. McIlleron, P.I. Folb, I. Ribeiro, F. Little, M. Gomes and M.E. Molyneux. Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study, *Lancet* **363** (2004), 1598–1605.

[4] R.O. Day, G. Shenfield, A.J. Smith, L.Weekes et al. The Quality in Australian Health Care Study (QAHCS): drug-related adverse events, Proc. Aust. Soc. Clin. Exp. *Pharmacol. Toxicol.* **13** (1996), Oral communication 17-3.

[5] T.P. de Vries, R.H. Henning, H.V. Hogerzeil, J.S. Bapna, L. Bero, K.K. Kafle, A. Mabadeje, B. Santoso and A.J. Smith. Impact of a short course in pharmacotherapy for undergraduate medical students: an international randomised controlled study, *Lancet* **346** (1995), 1454–1457.

[6] L. Donaldson and P. Philip. Patient safety – a global priority, *Bull. of the World Health Organization* **82** (2004), 892.

[7] M. Eddleston, L. Senarathna, F. Mohamed, N. Buckley, E. Juszczak, M.H. Sheriff, A. Ariaratnam, S. Rajapakse, D.Warrell and K. Rajakanthan. Deaths due to absence of an affordable antitoxin for plant poisoning, *Lancet* **362** (2003), 1041–1044.

[8] R. Laing, H. Hogerzeil and D. Ross-Degnan. Ten recommendations to improve use of medicines in developing countries, *Health Policy and Planning* **16** (2001), 13–20.

[9] W.G. McBride. Teratogenic action of thalidomide, *Lancet* 2 (1961), 1358.

[10] One module of the 12 that comprise the medical student programme can be accessed through http://nps.unisa.edu.au.

[11] E.E. Roughead, A.L. Gilbert, J.G. Primrose and L.N. Sansom. Drug-related hospital admissions: a review of Australian studies published 1988–1996, *Med. J. Aust.* **168** (1998), 405–408.

[12] E.E. Roughead and S. Semple (for the Safety and Quality Council). Second National Report on Patient Safety. Improving Medication Safety, *Australian Council for Safety and Quality in Health Care*, 2002.

[13] Uppsala Monitoring Centre. Annual Report of the UMC for 2003–2004, http://www.who-umc.org/umc.html.

[14] B.J. Vakil, T.H. Tulpule, D. Laurence and P.A. Armitage. Comparison of the value of 200,000 IU of tetanus antitoxin (horse) with 10,000 IU in the treatment of tetanus, *Clin. Pharmacol. Therap.* **9** (1968), 465–471.

[15] L.M. Weekes, J.M. Mackson, M. Fitzgerald and S.R. Phillips. National Prescribing Service: creating an implementation arm for national medicines policy, *Br. J. Clin. Pharmacol.* **59** (2005), 112–116.

[16] N.J. White. Twenty years of the Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme, *Southeast Asian J. Trop. Med. Public Health* **30** (1999), 216–219.

[17] R.M. Wilson, W.B. Runciman, R.W. Gibberd, B.T. Harrison, L. Newby and J.D. Hamilton. The quality in Australian health care study, *Med. J. Aust.* **163** (1995), 458–471.

[18] World Health Organization. Guide to Good Prescribing, WHO/DAP 94.11, World Health Organization, Geneva, 1994.

[19] World Health Organization. Guidelines for the development of national drug policies,World Health Organization, Geneva, 1988.

[20] World Health Organization. Counterfeit drugs. Guidelines for the development of measures to combat counterfeit drugs, WHO/EDM/QSM/99.1, Geneva, 1999.