The clinical pharmacologist in drug discovery and development

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- 1 Clinical pharmacology is a key activity in drug discovery and drug development with much to contribute to drug innovation.
- 2 However, very few clinical pharmacologists choose the pharmaceutical industry as their ultimate career.
- 3 Medical alumni of the RPMS clinical pharmacology department illustrate this; only four industrial careers *vs* thirty professors of clinical pharmacology or medicine.

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Introduction

I am delighted to have been asked to contribute a commentary on the role of the clinical pharmacologist in drug discovery and development to this festschrift for Sir Colin Dollery. I worked for Colin in the Department of Clinical Pharmacology at the Royal Postgraduate Medical School (RPMS), Hammersmith Hospital, London from 1969–1983. I began as house physician and bowed out as Senior Lecturer in Clinical Pharmacology. During the 14 year period I had a few spells away from the Hammersmith but I always felt myself to be on secondment from the main department. I greatly enjoyed my time in academic clinical pharmacology and I learned a great deal which has helped me in later life.

One of Colin's early lessons to me as a young research fellow was that every scientific communication must contain data. If an abstract contained no numbers and no statistics then it was of no interest and not allowed out of the department. This stricture has been ringing in my ears as I struggled with this paper.

How many clinical pharmacologists work in the pharmaceutical industry? What do they bring to the drug discovery and development process? What proportion of a new drug registration file is really clinical pharmacology? How many new drugs are designed using clinical pharmacological insights? These are the sort of hard data I hoped to gather. In the event, the literature contains virtually no reference to such issues, no answers and certainly no numbers. I have been forced to tackle the questions from my own experience and by consulting colleagues. I hope Sir Colin and any other readers will accept my qualitative development of the theme and cast a blind eye over the deficiency of hard data.

Credentials

If opinions and views are to be the main stuff of this contribution, then the reader is entitled to know the author's experience of the subject at hand, namely the inner workings of the pharma industry. Following my successive stints at the RPMS I have worked in industry for the last 12 years, first for a multinational US company, Merrell Dow, and latterly for a start-up biotechnology company, British Biotech. My two employers pretty well span the extremes of size and culture. I have had responsibility for most, indeed all, the R&D activities carried out in the industry, ranging from drug discovery, both chemical and biotechnological, to drug development and medical affairs. I have worked in the US and in Europe and been responsible for R&D in Japan. I have had most of the rites of passage, a major company merger, various downsizings, consolidations, acquisitions and a company flotation on the stock market. I have been dragged before an FDA advisory panel, been insulted by a French regulator, negotiated with Professor Poggolini and defended a class action suit. I have also had the very great satisfaction of bringing several novel therapeutics successfully to market and into widespread clinical use.

The paradox of clinical pharmacology

Clinical pharmacology is one of the most influential scientific disciplines within the pharmaceutical industry. Despite this, the industry employs rather few 'card carrying' clinical pharmacologists. This paradox is worth exploring since it gives an interesting insight into the

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structure both of industry and the attitudes of academic clinical pharmacologists.

Clinical pharmacology in industry

The primary motivation of the pharmaceutical industry is to return profits to its shareholders. By far the most efficient way of doing this is to discover and develop patented drugs which meet unmet medical needs and hence command high prices and high returns. The industry is closely regulated and to commercialize a new entity, a pharmaceutical company must convince drug regulatory authorities that the drug meets three criteria: efficacy, safety and quality.

Clinical pharmacology, as the science of drug actions in man, plays a central role in providing the evidence to satisfy each of these three criteria.

(1) Efficacy

Does the drug work? In theory, all that is required is to carry out two statistically acceptable clinical trials which demonstrate efficacy. In practice, this is never entirely sufficient; the reviewers need strong assurance that there is a good logic for the drug to work. No-one, even regulators, really believes in statistics. One key way of building the logical case is to prove that the drug is detectable in the patient and that it persists long enough to exert an action. This is a basic principle of clinical pharmacology or pharmacokinetics. Unfortunately some drugs have a persistent strong effect long after they cease to be detectable. This occurs with long-acting antihistamines where it has never been properly explained and it also occurs with irreversible inhibitors of enzymes where the rate of resynthesis of the enzyme determines the duration of drug action. It is an interesting insight into how firm the grip of pharmacokinetics is that it does prove difficult to get this 'hit and run' concept across.

Evidence of efficacy based on pharmacodynamics rather than PK analysis is less widely used. However, if it is possible to assay a drug effect in man other than the ultimate clinical outcome then this can make a clinical development project much easier to carry out. Data on dose, dosage interval and inter-individual variation are much easier to obtain in this way. For example, with receptor antagonists it may be possible to perform skin tests with the agonist and chart the time course and duration of drug action. The classic example is the weal and flare produced by intradermal histamine which can be used to measure antihistamine (H_1) effects. By analogy, soon after I joined Merrell Dow, I initiated a project with intradermal serotonin. This worked well with the 5-HT₃-receptor antagonists we were working on.

Pharmacodynamic assays are more difficult with enzyme inhibitors but *ex vivo* assays of enzyme activity in white blood cells can be useful. Increasing confidence in the use of cancer antigen levels as surrogate markers

of tumour progression has been crucial in dose finding studies of matrix metalloproteinase inhibitors in cancer. With antibiotics *ex vivo* assays are an important part of the clinical development phase and enable volunteer experiments to be done. If you can stop the bacteria of interest growing in a test tube by adding dilutions of serum from subjects treated with the drug then the clinical trial is a mere formality. This is the ideal position to be in. Unfortunately it is unusual; all too often the outcome of clinical trials, with all their erratic idiosyncrasies, becomes critical to the success or failure of a new drug.

(2) Safety

Clinical pharmacology, particularly pharmacokinetics, is a very important component of drug safety evaluation. Adverse events may be idiosyncratic but are mostly dose and plasma concentration related. The detection and avoidance of drug interactions leading to changes in the clearance of drugs is a growth area, particularly since the identification of specific hepatic cytochrome P450 subtypes has made the work easier to do *in vitro*.

(3) Quality

Here the impact of clinical pharmacology is perhaps the least since chemical and biological analyses of the drug product and its immediate precursors are the main focus. However, the proof of any dosage form is ultimately its administration to man and resulting PK analysis. 'Biobridge studies' to prove equivalency between the similar but slightly different formulations often used in clinical trials during a drug's development are key features of many drug applications.

In all these three aspects, the role of clinical pharmacology has been to check, elaborate and explain the activity of a new drug product. Has clinical pharmacology a more creative role in initiating new products or methods of treatment? Indeed it has, but this role is somewhat limited. Most new drugs still originate from screening procedures where very large numbers of chemicals are assayed against biological targets of interest. These used to be physiological changes in the whole animal but more recently the biotargets are likely to be more sophisticated enzyme array-type assays. The introduction of robotics and computerisation has greatly increased the productivity of such assays and hence their popularity. The use of combinatorial chemistry to synthesise large numbers of chemicals has fed into this process, enabling human thought to be hopefully eliminated from research in the larger pharmaceutical concerns. However, choice of the biotarget is still irritatingly critical and does require some limited insight into the clinical condition being addressed.

Clinical pharmacological insights leading to improved therapies could, and should, prove a source of new drugs but examples are rare. The development of a

methionine/paracetamol combination would be one example, use of very low dose aspirin for cardiovascular prophylaxis is another. However, such intelligent insights do not yield successful commercial products because they are not patentable. By the time a drug has been used long enough in clinical practice for a useful insight to be gained into how to improve it, there is no patent life left to exploit. As an example close to the RPMS department's main clinical interest, it is now known that we have been grossly overdosing hypertensive patients with thiazides for many years. Much smaller doses of these drugs than currently used are efficient at lowering blood pressure and are likely to have fewer metabolic effects. Nevertheless, no manufacturer has produced smaller dose formulations because thiazides are now generic and there is no commercial return to be gained from producing a low dose product and doing the necessary work to have it approved by the regulatory authorities. Perhaps there is a role here for an academic or health service initiative, actively producing and developing rational drugs rather than just bemoaning the lack of them.

Clinical pharmacologists and the pharmaceutical industry

One interesting paradox is that there are so few clinical pharmacologists employed in the pharmaceutical industry and yet clinical pharmacology is such an influential scientific discipline within the industry.

Here there are a few facts to illustrate the thesis. The pharmaceutical industry in the UK employs over 100 000 people. It is Britain's second most important exporter, after aerospace, and arguably Britain's most important revenue earner worldwide. However, a very small proportion of the employees are medically qualified and a still smaller proportion have had any formal training in clinical pharmacology.

Data are difficult to obtain but I can illustrate this by reference to the British Pharmacological Society which in 1994 had some 2116 ordinary members, of whom 621 worked in industry. Of the 621, only 32 had a formal training or background in clinical pharmacology. Closer to home, if one examines the careers of the medical alumni of the RPMS Clinical Pharmacology Department since 1966, an impressive number, some 30, has gone on to occupy chairs of clinical pharmacology or medicine worldwide. The roll call in the UK is well known; Newcastle, Liverpool, Glasgow, Cambridge, Southampton, Guys, etc. By contrast, only four medical alumni of the department have entered the pharmaceutical industry, a smaller number than those who have chosen general practice. Industry has been a very unpopular career choice.

It is interesting to speculate why this state of affairs exists. It always seemed to me personally that the most interesting aspect of drug research was to innovate, to discover and develop new drugs as new treatments for disease. The natural, indeed, only, practical setting for this activity is the pharmaceutical industry. No drugs originate in academic departments. In view of this, why

do so few of my peers want to work in industry, why do they prefer academic medical careers?

I think perhaps the main reason is the perception of prestige and academic independence. Industry and commerce are still regarded as slightly grubby and second rate in Britain. More practically, the academic ladder is well signposted and the rungs are clear cut. By contrast, industry appears a morass of different job titles and ill-defined responsibilities and these sorts of ambiguities are not at all attractive to the academic mind. The academic clinical pharmacology community regards industry as a good source of funds but not a serious option for a career.

Clinical pharmacology and R&D decisions

I am grateful to Professor Stuart Walker for some data on decision making in the industry. The Centre for Medicines Research conducted a survey in 1992 which investigated the way in which strategic decisions were taken by R&D managers. Some 45 R&D directors from major international companies responded to the survey, accounting for 75% of global R&D investment. There were 13 US companies, 10 Japanese and 22 European companies included. There is a wealth of detail in this survey which gives an insight into such disparate issues as the target times R&D directors were aiming for in drug development. It is an interesting feature of these sorts of surveys that while development times lengthen in response to increasing regulatory demands, the R&D directors always predict that development times will soon shorten, a triumph of hope over experience! However, of direct interest is the role clinical pharmacology played in making decisions on taking compounds from one phase of development onto the next. Clinical pharmacology played almost no role in decisions to take drug candidates through the early stages of exploratory research, synthesis and patent filing. Nor was clinical pharmacology much involved in decisions to take drugs into late stage clinical development, i.e. Phase III, NDA filing or marketing. However, some three quarters of R&D directors did take clinical pharmacology into account in decisions related to the early stages of clinical development, Phase I and Phase II. This corresponds to the stages of drug development when the first pharmacokinetic data become available and decisions based on bioavailability, clearance rates, metabolic fate, possibilities of drug interaction can be made. It should be added however, that commercial considerations and input from marketing had a far stronger overall input into all these decisions than did clinical pharmacology.

On this general topic, the influence of clinical pharmacology on decision taking in industry, it is perhaps worth making the point that the Boards of Directors of major pharmaceutical companies are not overly stocked with clinical pharmacologists or even technically qualified persons of any discipline. This is true both in the UK and in the US. In continental Europe a doctorate is not quite the same disqualification

for board service but again, there is little evidence that decisions are taken by directors of technical rather than commercial backgrounds.

There is one major exception to this trend and that is that biotech companies do tend, at least initially, to be technically driven and technically directed. Indeed, the motivation to 'start up' is often frustration at commercial lack of interest in technical ideas. However, once commercial success is achieved then the technical men tend to be succeeded by commercial directors and research once again becomes a back-room activity.

Negative influences

Despite all the foregoing comments, I would submit that the influence of clinical pharmacology on the pharmaceutical industry has not been completely positive. I would cite the increasing burden of regulatory requirements as having had at least a minor contribution from clinical pharmacology. The massive emphasis on pharmacokinetics, the tedious clinical trial designs and the fussy statistics, all these owe a little to my clinical pharmacological colleagues who sit in judgement in regulatory committees.

Another cross we have to bear in industry is the suspicious and cynical attitude of young prescribers and medical students towards the industry. During a recent

teaching session at Oxford to which I was invited to contribute, the third year medical students were so ignorant of the workings of industry that they debated the abolition of patents on pharmaceutical products as a means of reducing drug costs. My mild explanation that patents were simply a practical mechanism of attracting investment to therapeutic research was not well received. I do think that educators in clinical pharmacology should give their students some insight into the economics of innovation and not devote themselves entirely to presenting the case for generic prescribing!

Conclusion

The discovery and development of new drugs is a fascinating activity which I would not swap for any of the many alternative careers open to a well qualified clinical pharmacologist. It brings many rewards, not least the ultimate satisfaction of translating sales figures back into numbers of patients being treated with a new drug one has had a hand in introducing. Like hospital medicine, drug innovation is a team activity involving many disciplines. However, clinical pharmacology has a central role and I am very pleased with the uses I have been able to find for this discipline within the pharma industry.