Progress in clinical pharmacology over the last 20 years

Michel Eichelbaum

Dr Margarete Fischer-Bosch-Institute for Clinical Pharmacology, Auerbachstrasse 112, 70376 Stuttgart, Germany

The late 1950s and early 1960s witnessed a dramatic change in the practice of medicine. At this time many drugs were introduced into the clinic which for the first time allowed the effective treatment of many common diseases such as hypertension, angina pectoris, depression, schizophrenia, carcinomas and leukaemias to name only a few. Right from the beginning of modern drug therapy, it was observed that there was substantial variability among patients both in therapeutic efficacy and the occurrence of side-effects. The realization that dose was a poor predictor of therapeutic response raised the curiosity of clinicians and pharmacologists in elucidating the mechanisms responsible. This was the starting point for the development of clinical pharmacology. Of great importance for clinical pharmacology was the work carried out by the groups of R. T. Williams at St Mary's Hospital and B. B. Brodie in the Laboratory of Chemical Pharmacology at the NIH who pioneered the work on drug metabolism. The discovery of drug-metabolizing enzymes and realizing that their activity determined the rate at which drugs were eliminated from the body was instrumental for our understanding of why patients respond differently to the same dose of a drug. In a number of elegant studies, B. B. Brodie and coworkers showed that species differences in the duration of hexobarbitone action after administration of the same dose were not due to differences in sensitivity but a consequence of pronounced species differences in the rate of biotransformation of hexobarbitone. Moreover, he showed that the blood concentration at the time of awakening was very similar among the various species and in man. It is still worth reading his famous Toral Sollmann Award lecture *Of Mice, Microsomes and Man* at the ASPET Meeting (August 13, 1963). In this lecture, many principles that can account for variability in drug response between animals and humans were put forward. The concept that drug effects are not related to the dose administered but rather the plasma concentration achieved, and that in analogy to species differences, patient-to-patient variability in response can be explained by different plasma concentrations, was instrumental for clinical pharmacology.

Rather than giving a detailed account on the progress being made, I would like to focus on Alasdair Breckenridge's contribution to the field of drug metabolism. It is in the area of drug metabolism and especially in understanding the various factors that could affect the activity of drug-metabolizing enzymes where Alasdair Breckenridge has made substantial contributions to clinical pharmacology throughout his professional career. His interest was not restricted to the experimental findings but to explore the consequences of his results for drug action and side-effects in patients. It is a persistent feature of his work that observation of a clinical problem led him to carry out experimental work to understand the mechanisms responsible and then to test the hypothesis generated in his laboratory experiments in the clinical setting. His initial work in the area focused on the importance of drug metabolism for interindividual differences in drug kinetics as this was identified at this time as a major source of variability in response [4, 7, 11]. This work was consequently extended to the clinical setting when the role of pathophysiological factors influencing drug kinetics was studied [8].

At the same time that all the new drugs were introduced into clinical medicine, it was realized that coadministration of two or more drugs could result either in an increased or a diminished drug action, a phenomenon termed drug interaction. It was soon realized that changes in drug metabolism were a major mechanism due to either inhibition or induction of drug-metabolizing enzymes [4, 10]. Particularly in the case of the oral anticoagulant warfarin, these metabolic interactions had detrimental consequences for the patients. It was Alasdair Breckenridge and his coworkers who were at the forefront, and made major contributions to our understanding of warfarin interactions [1, 4]. In addition, in work carried out together with Edgar Ohnhaus, Alasdair not only explored the role of rifampicin in the induction of drug-metabolizing enzymes but also its physiological functions. They demonstrated for the first time that induction by rifampicin increased liver blood flow substantially [13].

Although the clinical importance of drug interactions have been recognized and the principal mechanism elucidated many years ago, they continue to be a relevant problem. Every year drug interactions lead to the withdrawal of medicines from the market.

Correspondence: Professor M. Eichelbaum, Dr Margarete Fischer-Bosch-Institute for Clinical Pharmacology, Auerbachstrasse 112, 70376 Stuttgart, Germany. Email: michel.eichelbaum@ikp-stuttgart.de

Received 16 December 2002, accepted 27 January 2003.

In the 1980s, chirality of drug action and disposition became a big issue in clinical pharmacology, industry and regulatory agencies. It was the late pharmacologist E. J. Ariëns who questioned the use of racemates by phrasing it this way: 'Consumers have long been asking for clean water and clean food. Next they will ask for clean drugs'. He was referring to the situation that, in contrast to drugs derived from natural sources which are usually administered as pure enantiomers, most of the drugs produced by chemical synthesis are racemates, e.g. a 50 : 50 mixture of two enantiomers. Because the enantiomers contained in racemates quite often differ both in qualitative and quantitative terms in their pharmacological activity and kinetic behaviour two drugs are in fact being administered. Thus in the case were one enantiomer is much less potent than the other, Ariëns considered this enantiomeric ballast, which was responsible for adverse effects of racemates [1]. This two-faced nature of racemates and its consequences for drug action and disposition, especially in the context of drug interactions with warfarin, was already realized by Alasdair and his group in the early 1970s. In 1973, in a classical work with warfarin they studied the kinetics and dynamics of R- and S-warfarin demonstrating that they behaved quite differently [6]. Moreover they showed that the R and S enantiomer were metabolized by different routes. By applying this knowledge, they could explain the paradoxical observation that there were drug interactions with warfarin that caused a dramatic increase in the anticoagulatory effect without affecting the drug concentrations. Based on a careful analysis of the kinetics and of the metabolites formed from R- and S-warfarin, the hypothesis was put forward that phenylbutazone affected the metabolism of R- and S-warfarin in opposite directions, i.e. inhibition of S- and induction of R-warfarin clearance. They also realized and demonstrated that changes in protein binding, which at that time were considered as the mechanism responsible for the phenylbutazone-warfarin interaction, were unlikely [9, 12].

In the late 1970s and early 1980s our understanding of drug metabolism and its contribution to presystemic elimination changed. At this time it was increasingly recognized that in addition to the liver, gut wall was an important site of drug metabolism. Again Alasdair Breckenridge was active in the field right from the beginning, studying the contribution of gut wall to the presystemic metabolism of ethinyloestradiol and norethindrone. In these studies he and his coworkers showed that there was substantial conjugation by the gut wall of these drugs and outlined that this accounted for the rather low oral bioavailability of this class of compounds [2, 3, 10].

Since that time, our understanding of the processes involved in the absorption, distribution, metabolism and elimination of drugs has advanced substantially, especially

in the area of drug absorption, which until recently had been considered a passive process depending on dissolution of the drug preparation, particle size, physical chemical properties such as lipophilicity and the pK_a of the drug. It is now known that this process is controlled by active transport.

In summary, this brief overview demonstrates the progress that has been made in drug metabolism during Alasdair Breckenridge's professional career. It shows the constant progress that has been made over the years by adding more and more details to give a very complex picture that at the beginning was a rather simple sketch. Clinical pharmacology owes Alasdair Breckenridge much for the many valuable pieces he has contributed in creating this picture.

References

- 1 Ariëns EJ. Nonchiral, homochiral and composite chiral drugs. *Trends Pharmacol Sci* 1993; **14**: 68–74.
- 2 Back DJ, Breckenridge AM, Crawford FE, Orme ML'E, Rowe PH, Smith E. First-pass effect of norethindrone in rabbits and rats. *J Pharmacol Exp Ther* 1978; **207**: 555–565.
- 3 Back DJ, Breckenridge AM, MacIver M, *et al.* The gut wall metabolism of ethinyloestradiol and its contribution to the pre-systemic metabolism of ethinyloestradiol in humans. *Br J Clin Pharmacol* 1982; **13**: 325–330.
- 4 Breckenridge A, Orme M. Clinical Implications of enzyme induction. *Ann NY Acad Sci* 1971; **179**: 421–432.
- 5 Breckenridge AM, Challiner M, Mossman S, *et al.* Cimetidine increases the action of warfarin in man. *Br J Clin Pharmacol* 1979; **8**: 392–393.
- 6 Breckenridge AM, Orme M, Wesseling H, Lewis RJ, Gibbons R. Pharmacokinetics and pharmacodynamics of the enantiomers of warfarin in man. *Clin Pharmacol Ther* 1974; **26**: 424–430.
- 7 Breckenridge AM. Antipyrine half-life and drug elimination. *Clin Pharm* 1980; **5**: 201–203.
- 8 Breckenridge AM. Pathophysiological factors influencing drug kinetics. *Acta Pharmacol Toxicol* 1971; **29**(Suppl 3): 225–228.
- 9 Choonara IA, Cholerton S, Haynes BP, Breckenridge AM, Park BK. Stereoselective interaction between the R enantiomer of warfarin and cimetidine. *Br J Clin Pharmacol* 1986; **21**: 271–278.
- 10 Crawford FE, Back DJ, Orme ML'E, Breckenridge AM. Oral contraceptive steroid plasma concentrations in smokers and non-smokers. *Br Med J* 1981; **282**: 1829–1830.
- 11 Davies DS, Thorgeirsson SS, Orme M, Breckenridge AM. Interindividual differences in rates of drug oxidation in man. *Drug Metab Dispos* 1973; **1**: 411–417.
- 12 Lewis RJ, Trager WF, Chan KK, *et al.* Stereochemical aspects of its metabolism and the interaction with phenylbutazone. *J Clin Invest* 1974; **53**: 1607–1617.
- 13 Ohnhaus EE, Thorgeirsson S, Davies DS, Breckenridge AM. Changes in liver blood flow during enzyme induction. *Biochem Pharmacol* 1971; **20**: 2561–2570.
- 14 Serlin MJ, Mossman S, Sibeon RG, *et al.* Cimetidine: Interaction with oral anticoagulants in man. *Lancet* 1979; **ii**: 317–319.