Editors' view

Concentration-effect and dose-response relations in clinical pharmacology

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The action of a medicine on one organ rather than on another is accounted for on the chemical hypothesis, by assuming the existence of unequal affinities of the medicinal agent for different tissues.

Jonathan Pereira, *The Elements of Materia Medica*, 1854

The importance of the dose-response curve, or concentration-effect relation, in pharmacology is perhaps most strikingly reflected in the fact that in the year in which the British Pharmacological Society was founded, 1931, A J Clark, at that time Professor of Materia Medica [i.e. Clinical Pharmacology] in the University of Edinburgh, was elected to a Fellowship of the Royal Society for his contributions to the quantification of drug-receptor interactions.

In 1905 J N Langley, Professor of Physiology in Cambridge, suggested that what he called 'receptive substances' were responsible for the effects of nicotine and curare on skeletal muscle [1]: 'In all cells two constituents at least must be distinguished, (1) substances concerned with carrying out the chief functions of the cells . . . and (2) receptive substances especially liable to change and capable of setting the chief substance in action' [2]. Then Paul Ehrlich, who had coined the term 'receptor' in 1900 in relation to his chemical side-chain theory of immunity, coined the term 'chemoreceptors' in his Harben Lectures of 1907 [3]: 'I have now formed the opinion that some of the chemically defined substances are attached to the cell by atom groupings that are analogous to toxin receptors; these atom groupings I shall distinguish from the toxin receptors by the name "chemoreceptors".'

A V Hill, a student of Langley's in Cambridge, explored the concentration-effect curve quantitatively in 1909, resulting in the well known Hill or Hill-Langmuir equation. However, it was A J Clark [4] who applied this

more generally to concentration-effect curves, in what is now known as classical receptor theory. Clark assumed that the effect of a drug is directly proportional to the concentration of drug-receptor complex and that the maximum effect occurs when all the receptors are occupied. From this he derived the apparent dissociation constant of the interaction of a drug with its receptor. The quantitative analysis of competitive antagonism by the 'dose ratio' method was introduced by J H Gaddum, who was at the time Professor of Pharmacology at University College London [5], and was later elaborated by H O Schild [6], who was to become one of Gaddum's successors at UCL. Classical theory was later extended by the Dutch pharmacologist E J Ariëns, who used the term 'intrinsic activity' to describe the proportionality constant relating effect to the concentration of drug-receptor complex [7].

Modifications to classical receptor theory came when its basic assumptions were questioned, at first by R P ('Steve') Stephenson from Edinburgh, who showed that the assumption of proportionality between occupancy and effect was incorrect, and postulated [8] that a maximum effect can be produced without total occupancy of receptors (spare receptors). He coined the term 'efficacy' as a measure of the ability of a drug to activate receptors and cause a response. Other later developments, too many and complex to detail, included Paton's rate theory [9], Changeux's allosteric theory [10], and the elucidation of models to try to explain the difficult concept of efficacy [1]. Add to this the various behaviors of G-protein-coupled receptors, related to spontaneous production of receptor active states, ligand-selective receptor active states, oligomerization with other proteins, and allosteric mechanisms [11], and the increasing complexity of the subject can be readily appreciated. The observation of hormesis, in which there are stimulatory effects at low concentrations and inhibitory

Figure 1

The effect of thyroid extract in the treatment of hypothyroidism [4]

effects at high ones [12], adds an extra dimension, which is not vitiated by its uncritical adoption by the homoeopathic lobby. Indeed, it is salutary that A J Clark's contribution to receptor theory was important in debunking homoeopathic theories of the time [11].

It is striking, as one looks through the literature on dose-response and concentration-effect relations, that the vast majority have been derived from studies in cells or tissues in vitro or from experiments in animals. There are relatively few sets of pharmacodynamic data derived from human experiments across wide ranges of concentrations or doses. An early exception to this, from the work of A J Clark, is shown in Figure 1. Notable later examples include the relation between urinary concentrations of loop diuretics and their effects on the rate of urinary sodium excretion [13, 14] and that between plasma propranolol concentrations and the effect of propranolol in reducing exercise-induced tachycardia [15]. Even so, the latter extends only over the linear part of the sigmoid logarithmic concentration-effect curve.

It is very encouraging, therefore, when dose-response or concentration-effect relations appear in the *Journal*. Last month, for example, I highlighted evidence that headache due to calcium channel blockers is dose-related in the therapeutic range of doses [16], as is cardiac arrest in hospital associated with the use of non-antiarrhythmic drugs that prolong the QT interval [17]. However, in vivo evidence of this sort is hard to come by, because it is not often possible to obtain data from patients taking a sufficiently wide range of doses or with a sufficiently wide range of plasma concentrations for comparison with measured effects; it is not surprising that the first of these studies was a meta-analysis and the second a case-control study. In this issue Sudhakaran et al. show how this problem can be tackled by combining in vitro and in vivo studies, at least in relation to a pharmacokinetic variable that is relevant to pharmacodynamics [18]. They measured the protein binding of indinavir and saquinavir in vitro across a range of protein concentrations and in vivo in paired fetal and maternal plasma samples in women with and without HIV infection. Differential binding of the two drugs, largely attributable to the transplacental concentration gradient of α_1 -acid glycoprotein, was thought to contribute to the low cord to maternal total plasma concentration ratios of these antiretroviral protease inhibitors. The importance of α_1 -acid glycoprotein in determining drug disposition is not often given prominence, but these results are clearly relevant to the use of these protease inhibitors in preventing transmission of HIV from mother to child.

Elsewhere in this issue of the *Journal* McQuay & Moore show how it is possible to uncover the nature of the dose-related effect of analgesics. From a meta-analysis of 50 randomized double-blind trials in patients with acute pain, and relatively limited dose-related data, they were able to make conclusions about the steepness of the dose-response curves with aspirin, ibuprofen, and paracetamol [19]. They suggested that the dose-response curves were not steep, showing a 10% increase for a doubling of dose. However, if this effect was on the linear part of the logarithmic curve, the whole curve would be complete over about two orders of magnitude, which a pharmacologist would not consider to be shallow. Nevertheless, it is certainly less steep than the dose-response relation produced by opioid analgesics, as one would expect. Other aspects of these results are discussed in an accompanying commentary [20], in which Alain Li Wan Po demonstrates beautiful dose-response data for ibuprofen from elsewhere, showing a 60% increase in effect over only one order of magnitude of changing dose. The problems of generating dose-response curves in this difficult area have by no means

been overcome, but this work is a step in the right direction.

We need many more such studies. Data obtained in humans during drug development will always generate information about how pharmacokinetics vary with dose, but little information on pharmacodynamic variability and virtually no information on adverse effects. Large observational studies and systematic reviews of published data aimed at elucidating the relationships will help, as may in vitro–in vivo correlations. It might also be useful to create a database of published dose-response and concentration-effect curves in humans, to document the shape and steepness of individual curves and to show how they differ in different circumstances. We should be more receptive to Langley's receptive substances.

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