



Dose optimization in drug development: role of phase IV trials

Pieter H. Joubert

Head Clinical Pharmacology, Clinical Science Department, F. Hoffmann-La Roche, 4002 Basel, Switzerland

Abstract

Intense competitive pressure may require short development times and can result in approval of safe and effective dose regimens that are suboptimal. Well-designed phase IV studies can lead to identification of doses and dose regimens that may improve efficacy and/or reduce risks (resulting in an improved risk/benefit ratio). Furthermore, new indications can be explored and new dose regimens and formulations may be developed to optimize therapy and patient compliance. *Improved efficacy*: The efficacy of HIV-protease inhibitors (e.g., saquinavir) has been improved by formulations or combinations exhibiting higher bioavailabilities. For lisinopril, a large phase IV trial showed that a dose much higher than that widely used was necessary to reduce mortality in patients with congestive heart failure. *Reduced risk*: Captopril, the first angiotensin-converting enzyme (ACE) inhibitor to reach the market was initially marketed at too high a dose. A reduction in dose markedly reduced the risk of nephrotoxicity while maintaining anti-hypertensive efficacy. *New indications*: There are numerous examples such as the expansion of indications of beta-adrenergic blockers, calcium antagonists, and ACE inhibitors. *New dose regimens*: With saquinavir, it was possible with phase IV studies to demonstrate that efficacy (in terms of viral load) achieved with a three-times-daily regimen was maintained by a twice-a-day regimen. With nifedipine, it was shown that with slow infusion, there was effective blood pressure lowering and no compensatory tachycardia, whereas rapid infusion led to tachycardia with no blood pressure lowering. This allowed the development of a highly successful slow-release formulation. Successful registration of a new medicine is not the end of the drug development process but a gateway to intelligent life cycle management aimed at optimizing patient benefit. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Phase IV; Post-marketing; Life cycle management; Formulation; Risk–benefit

E-mail address: pieter.joubert@roche.com (P.H. Joubert).

1. Introduction

In spite of the rigor and competitiveness with which drug development is currently performed, pressure on timelines and resources require focussed and streamlined approaches looking at priorities. At the time of approval and launch of a product, there may often be many unanswered questions. Furthermore, with day-to-day use of a new product in practice, the situation is very different compared to the controlled environment of clinical trials. The post-approval period (phase IV) is consequently a very important time for increasing the knowledge base with respect to new drugs. This is the time when issues not apparent in the clinical trial environment might appear, and questions not addressed during a frantically paced drug development program can be investigated. Key sources of useful information during this period are post-marketing surveillance, spontaneous case reports, and phase IV studies in healthy volunteers and patients. This review will focus on the contribution that formal clinical trials can bring in the post-registration period.

There is a spectrum of consequences that may result from intense competitive pressure and short development times (Fig. 1). Although a safe and effective dose regimen may be approved, at one extreme, a "one dose fits all" approach with emphasis on efficacy can result in pivotal trials with a single high dose (e.g., the maximum tolerated dose) leading to an approved label which does not allow individualization of therapy. This could result in an incidence of adverse events which is higher than necessary. At the other extreme, physicochemical properties of a compound or practical restraints during development may prevent the full dose-response relationship from being adequately characterized resulting in an approved dose that is too low for optimal efficacy.

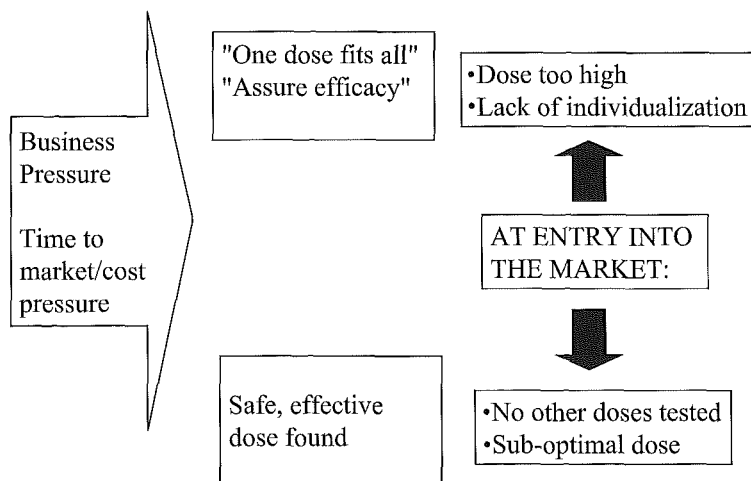


Fig. 1. Business, time and resource pressure may result in drugs being approved at doses that might not be optimal

Well-designed phase IV studies can lead to identification of doses and dose regimens that may improve efficacy and/or reduce risks (resulting in an improved risk/benefit ratio). Furthermore, new indications can be explored and new dose regimens and formulations may be developed to optimize therapy and improve patient compliance.

There are many historical examples of drug dosages and regimens changing as experience with a drug accumulates. Initial use of digitalis involved escalating the dose until toxicity occurred. This was then adapted to rational dose selection based on factors such as renal function and electrolyte status. A further example is the realization that low doses of thiazide diuretics have a minimal risk of electrolyte disturbances and adverse effects on glucose metabolism and lipid profiles while maintaining anti-hypertensive efficacy.

2. Discussion

In this section, I will review a number of examples from diverse therapeutic areas to illustrate how during phase IV, efficacy was improved or safety risk reduced (improved risk benefit), new indications emerged and improved dose regimens emerged. As all these factors impact on each other, many of the examples could fit into more than one of these categories. For a particular example, however, I have focussed on a characteristic appropriate to the heading.

Improved efficacy: In the human immunodeficiency virus (HIV) field, the efficacy of protease inhibitors, such as saquinavir, has been improved by formulations exhibiting higher bioavailabilities and by using a drug–drug interaction (combination with ritonavir) to increase exposure. The first protease inhibitor registered for the treatment of infections with HIV saquinavir [1] was formulated in a hard gelatin capsule with limited systemic availability [2]. As saquinavir has a large safety margin and the relationship between exposure (area under the concentration curve, AUC) and efficacy has been demonstrated [2], various avenues have been examined to improve bioavailability. One was the development and registration of a soft gelatin capsule [2] with enhanced bioavailability. A second avenue pursued for several protease inhibitors has been the use of a co-administered inhibitor of cytochrome P450 to reduce first-pass metabolism. When saquinavir is administered with a low dose of ritonavir, the AUC is increased without a worsening of the adverse event profile (Fig. 2). With higher doses of ritonavir, the effect on saquinavir AUC plateaus and the adverse event profile worsens [3]. This increase in exposure is reflected in enhanced efficacy [4]

Angiotensin-converting enzyme (ACE) inhibitors have become a cornerstone of modern therapy of congestive cardiac failure. Although it is easy in practice to titrate dose against symptomatic response, it is clear that symptomatic improvement is not always reflected in a reduction in mortality. A recently published study by Paredes et al. [5] examined the effect of the commonly prescribed low dose (2.5–5 mg daily) of lisinopril vs. high doses (32.5–35 mg daily) in 3000 patients with class II to IV heart failure (New York Heart Association). They demonstrated (Fig. 3) that with the higher

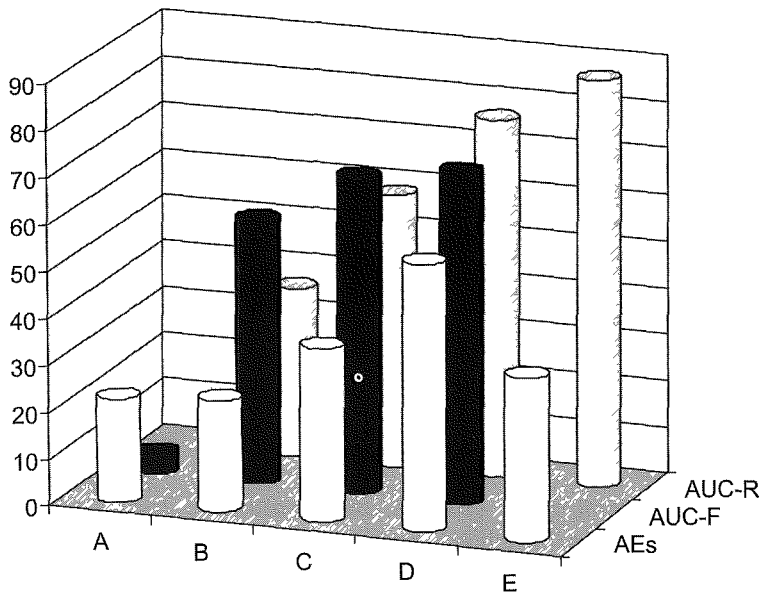


Fig. 2. Effect of saquinavir alone and in combination with various doses of ritonavir on number of adverse events (AEs), saquinavir AUC (AUC-F) and ritonavir AUC (AUC-R). (A) saquinavir 800 mg, (B) saquinavir 800 mg plus ritonavir 200 mg, (C) saquinavir 800 mg plus ritonavir 300 mg, (D) saquinavir 800 mg plus ritonavir 400 mg, (E) ritonavir 400 mg.

dose, the overall risk of death and hospitalization was reduced by 12% and the risk of hospitalization due to heart failure by 24%.

2.1. Reduced risk

In terms of basic pharmacological principles, if one wants to have the maximum therapeutic effect of a drug, a dose or exposure on the plateau of the dose or concentration effect curve needs to be used. The further to the right the dose is on the plateau, the greater the safety risk, particularly if the drug has a narrow therapeutic index (Fig. 4). Renal toxicity with deteriorating renal function may occur with the use of ACE inhibitors [5]. Captopril, the first angiotensin-converting enzyme (ACE) inhibitor to reach the market, was initially used at too high doses (probably far to the right in the dose-effect curve plateau) and a reduction in dose markedly reduced the risk of nephrotoxicity while maintaining anti-hypertensive efficacy.

Another very good example is nifedipine, where it was shown that the rate of administration was an important determinant of tachycardia as an adverse event [6]. When given at a slow infusion rate, blood pressure lowering occurs without the development of tachycardia. When infused rapidly, to the same steady-state concentration, reflex tachycardia occurs and the blood pressure is not lowered. This finding led to the development of a very successful slow-release formulation.

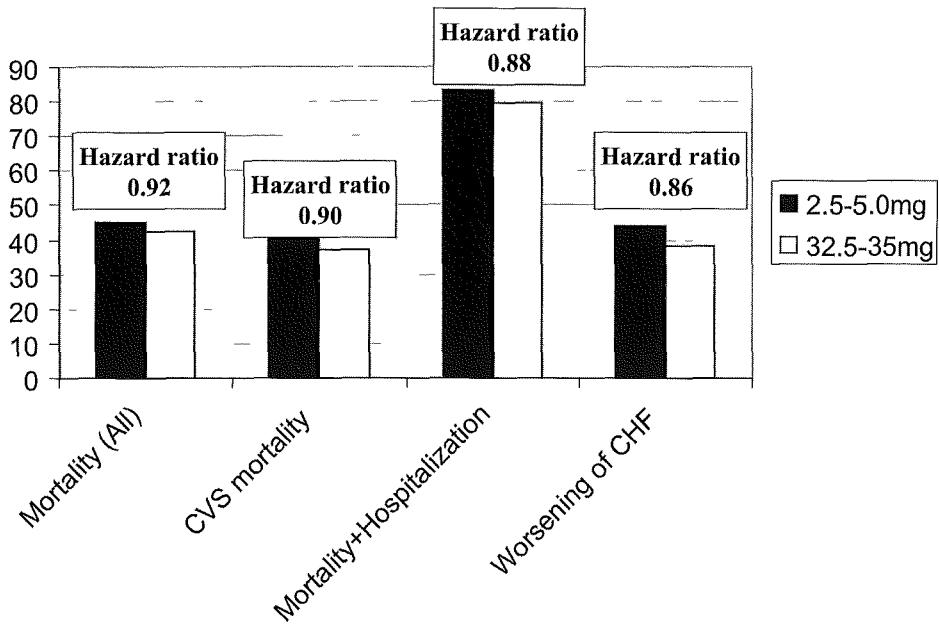


Fig. 3. Comparison of low- and high-dose lisinopril in congestive heart failure (CHF).

2.2. New indications

Budgetary restraints, timelines, regulatory hurdles and the size of the potential market usually result in drug development plans that focus on a single or a limited number of indications. It is also, in general, easier to develop drugs with symptomatic short-term

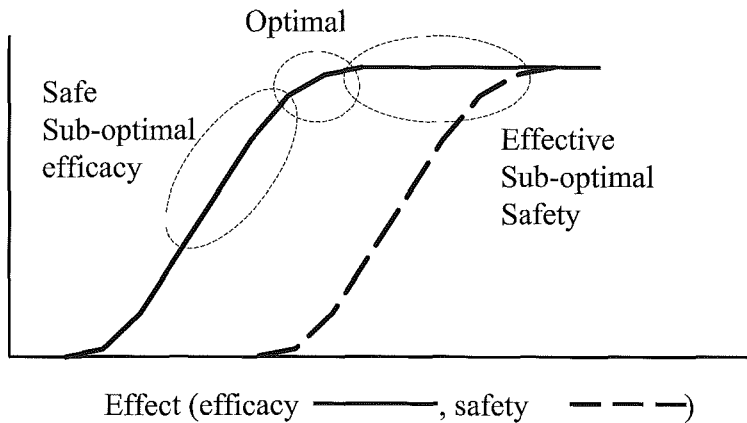


Fig. 4. A clear identification of the dose (or concentration)/effect relationship is necessary to optimize dosage.

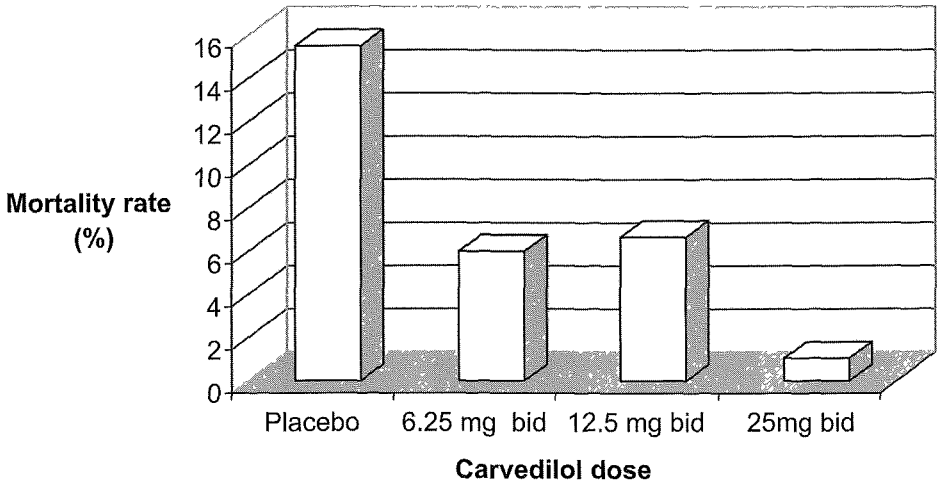


Fig. 5. Dose/effect relationship of carvedilol for mortality rate in congestive cardiac failure.

endpoints than for endpoints that require very large and long studies (with the associated restrictions in the approved labelling). Examples are blood glucose control vs. the development of long-term diabetic complications, symptomatic control of heart failure

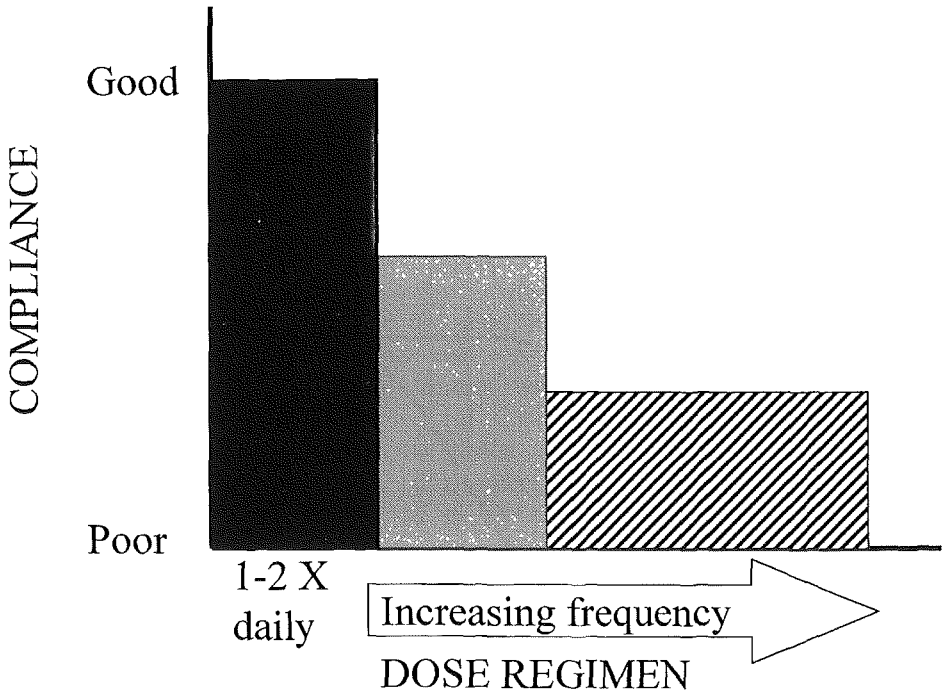


Fig. 6. Theoretical representation of the relationship between dosing frequency and compliance.

vs. reduction of mortality, bone mineral density determinations in osteoporosis vs. fracture rates, etc.

There are numerous examples of drugs that were brought to the market with limited indications which were expanded as new information became available. The ACE inhibitors were initially used for the treatment of hypertension, but have been shown to retard the development of microalbuminuria in patients with diabetic nephropathy and slow the deterioration of renal function [7]. The study showed a 50% reduction in the combined endpoint of deaths, dialysis and transplantation. These favourable effects occur over and above the effect on blood pressure control.

The use of beta-adrenergic blockers has through the years expanded to many indications such as hypertension, angina, tachyarrhythmias, tremors, hyperthyroidism and panic attacks. An interesting feature is that whereas beta-blockers were initially contra-indicated in patients with congestive heart failure, better understanding of the pathophysiology and additional studies have shown benefit. Benefit has, for instance, been shown with propranol in congestive cardiomyopathy [8]. Carvedilol has been shown to not only improve left ventricular function but to decrease mortality in patients with congestive cardiac failure. In a study by Bristow [9] in patients with stable mild to moderate congestive heart failure (stable diuretic and ACE inhibitor therapy), the all-cause mortality risk was reduced by 73% compared to placebo (Fig. 5).

2.3. New dose regimens

There is a clear relationship between frequency of drug administration and patient compliance (Fig. 6). This is particularly noticeable when changing from twice-a-day dosage to more frequent dosages [10,11]. With saquinavir, it was possible with phase IV studies to demonstrate that efficacy (in terms of viral load) achieved with a three-times-daily regimen was maintained by a twice-a-day regimen [12]. The findings with nifedipine [6] that lead to the development of a highly successful slow-release formulation have already been alluded.

3. Conclusions

It is clear, from the perspective of a drug developer, that successful registration of a new medicine is not the end of the drug development process but a gateway to intelligent life cycle management aimed at optimizing patient benefit and assuring commercial viability.

Appendix A. Discussion 5

D. Mould: I was wondering if you had any estimates of the percentage of compounds that are filed that eventually require dose adjustment in the post-marketing phase, and what the ultimate cost of making these labelling changes is for the pharmaceutical industry. It seems to me that once a compound has been approved and is on the market, usually, the pharmaceutical industry is very reluctant to make changes in the dosing at that point.

P. Joubert: This sounds like a typical Louis Lasagna question. I do not have any data, but I think this would be an excellent study to perform. Within my own drug development experience, from the clinical pharmacology point of view, we have had strong arguments that for a number of compounds the dosage regimen should be different to the one proposed for phase III, but once a phase III program has been commenced or completed, it is very tough to convince upper management to go back and redo it with a different approach.

D. Mould: Doesn't this sort of experience argue for somewhat slower drug development rather than for fast drug development?

P. Joubert: Yes and no; with the anti-flu drug that we developed in competition with Glaxo, they started ahead of us, but we came into the market very shortly after them and captured a large slice of the market. We could not afford to spend 2 years longer. It really depends on the competitive environment. If you have a new breakthrough drug and there is no competition, then I think it is really worthwhile extending the development time if it is within a new indication area, a new mechanism and this would enhance the quality of development. On the other hand, if you have a me-too drug, then you have to go as fast as possible, for business reasons.

A. Bye: I think Diane's got an extremely valuable point, if you get the dose wrong, the compound goes off the edge of the cliff, and you can't recover it. Sometimes that happens for very obvious reasons, like a QT effect for example.

P. Joubert: In the two concentrations or dose-effect relationships that I showed for efficacy and safety, your compound has a better chance of survival if you come out with a sub-optimal efficacy and a very safe drug, than coming out with maximal efficacy but a safety problem. An example that I dealt with as a drug legislator was Lilly's benoxaprofen, which was an excellent drug for rheumatoid arthritis. I think it's the sort of drug that should have been on the market, but it came out with too high a dose for elderly people with poor renal function and some people died. Once this happened, there was no way to rescue the drug although recurrence of the problem could have been prevented by appropriate labelling.

P. Morgan: I thought it was a fascinating example of using ritonavir to improve the AUC of saquinavir. Can you comment on whether or not that sub-therapeutic dose of ritonavir (200 mg) actually causes drug-drug interactions with other agents? Secondly, do you think that the use of an inhibitor is justifiable in non-life-threatening diseases?

P. Joubert: I don't think it's justifiable in non-life-threatening diseases because you have the same potential for interaction with saquinavir that you would have with co-medications. So, I think it is an approach you can only follow in a life-threatening disease where there is a problem.

L. Sheiner: It seems that a drug should be available to people who can benefit from it as soon as our state of information is such as to suggest that there is considerable likelihood of benefit rather than harm. That doesn't necessarily mean we have sufficient information to optimise use. However, there are two problems with relying on post-approval studies to determine conditions of optimal use. One is that there are very few pressures on manufacturers after drug approval, other than societal pressures, to get things right. Second, while it is true that without any clinical trials, without any formal organisation, the right dose generally does eventually emerge for useful drugs, and you

showed examples of this, nonetheless, this is at best an inefficient optimisation system. Is it your opinion that there's nothing we can formally do to increase the rapidity with which we get to optimal doses or best combinations? Or is there something we could do as a society or that the pharmaceutical industry could do that would make this happen faster?

P. Joubert: I think there are two things. I've seen the voice of clinical pharmacology grow in stature in the 10 years that I've been in the industry. When we made a statement on dosage and efficacy 5 or 6 years ago, it was seen as academically very nice and interesting, but our therapeutic colleagues knew or thought they knew what to do based on empirical clinical "gut" feeling. This has evolved into a situation now where PK/PD modelling and clinical trial simulation is becoming more important. So, I think it is being accepted into the process, and we are going to see a much better refinement of dosage during drug development. The other thing that has happened is that in some companies, project teams that used to hand drugs over to business at the time of registration now extends their activity into life-cycle management. A clinical pharmacologist is involved well before entry-into-humans and in phase II, already talks about life-cycle development. If there are issues in dosage development for phase IV, it is part of the planning. There is a prospective element to it now. I think, in the past, we burnt our fingers and we have to change. The prospective realisation of this is important and the role of PK/PD and clinical trial simulation is being established. I am confident that things are changing.

H. McQuay: It's strange to me that nobody brought in the fashion bit about outcome measures. In Europe, we have the fourth hurdle, we want to know how much change matters to patient and carer. It's particularly relevant to Keith's talk that those kind psychotestings are like kicking the tires to see what's wrong with the engine. What I want to know is what matters, what degree of change is there in the dementia outcomes at 6 months, and how much change matters to the patient and to the carer. It's relevant to me in the pain area. The second one is that, so often, we put up the slides on compliance, and it actually depends on what's wrong with you. If you have an outcome that is immediately altered as the drug wears off, you are compliant. If you hurt like hell after 4 h, you take the drug, and I think sometimes we need just to pause on that. So give me a really effective analgesic, but you have to take it every 4 h; and that's quite different from anti-hypertensive medication.

A. Bye: However, we don't normally log those differences in many cases. You tend to find now in the competitive market situation that those percentage differences are what differentiate one medicine from another. We've got two agents out there for flu, more or less both doing the same job, and the differentiator is actually a convenience kind of dosing, not the final outcome to the patient. I think it is an important point which people are latching onto.

H. McQuay: Sorry, which is why I think it should be built-in from the beginning.

P. Joubert: I also have this problem as a clinical pharmacologist. If you need a 10-thousand-patient study to show a 2% difference, I am asking myself about the real clinical benefit, but this is what is needed to get the drug registered. It is very tough to compare statistical and clinical significance in certain outcome measures. The flu story was again an argument, how does one judge the clinical benefit of a day less of symptomatology?

H. McQuay: The best example is the donepezil drug, where you've got a four-point shift on a 70-point scale. It is assumed that that is of no relevance to the patient or the carer, therefore, we will not buy the drug.

G. Levy: Just another variant of that is the current absence of comparative studies between a new drug and a presently available drug with similar indications. The question is, will the usually very large cost-differential be justified in terms of the difference in efficacy or safety? As a member of the editorial board of *The Medical Letter*, I'm up against this all the time. There's a reluctance by industry to do comparative studies. For decision-making, and in terms of pharmacoeconomics, this becomes a real problem.

P. Joubert: I agree with you. I also think the culture is changing. In the past, I had an uphill battle in early human studies to include comparators, and again recently we've been able to do this, and in fact we have been able to kill compounds in the first or second human studies.

S. Jackson: I absolutely agree with your comments about the frequency of dosing and its association with compliance, but you rather argued that there must be a scientific basis to suggestions that once a day is better than twice a day. What I would say is the burden of tablet-taking as opposed to compliance—compliance being whether or not you take your tablets—is how much you don't like doing so. I think when one looks at those sorts of things, and I agree it's not part of normal routine assessments, if you ask patients between once a day or twice a day, they will say "once a day", in the vast majority cases. I would like to see that the industry would start to collect data on that.

P. Joubert: I agree, it has not been studied scientifically, but my marketing colleagues assure me that if all things are equal, whether the doctor prescribed the drug or the patient takes it, you've got a better market share with once-a-day dosage.

K. Wesnes: The issue has been raised during the discussion of the overall clinical relevance of the end points we use in clinical trials. Obviously, I would be interested in defending cognitive function. Clearly there's a dissatisfaction with the quantum of improvement on the ADAS-Cog of anticholinesterases, i.e. what does a four-point shift in a 70-point scale signify and what does it represent in true behavioural terms? I think our responsibility as purveyors of dynamic measures is to convince people that what we are measuring has relevance, and to actually give a guideline to the extent of the changes in terms of their consequence for everyday life. Our approach to the problem has been that we have a large normative database and a large database of what Alzheimer's disease is. For example, in the trials we've conducted on anticholinesterases, we can pinpoint where the patient group starts off in terms of the amount of impairment they have compared to aged-match controls. After a period of treatment, we can see the extent to which they've moved towards a normal population for their age. Interestingly, when you start measuring attention and things which the ADAS-Cog does not measure, and you factor those into the equations, you can get improvements back towards normality of between 40% and 50%, with galanthamine or other anticholinesterases. I think we would all feel comfortable in saying that this is a behavioural shift (clinical effect) which we would think would be worth having. I think once automated systems with more extensive databases become involved in clinical trials, regulatory authorities will have more information on which to base the decisions to approve anti-dementia drugs or not.

P. Joubert: I agonise with what really is a meaningful increase or improvement in cognitive function in the Alzheimer's setting. I think, once you get to mortality and much harder end points, it is easier. In the area of cognitive or subjective function and quality of life area and so on, it is very tough to quantify benefit. Even with mortality, which is a hard endpoint, there are problems. In oncology, for example, if a drug improves survival by 3 months, how do you measure whether these 3 months are of value or not vs. the adverse event profile of the chemotherapeutic agents? You are in a very tough setting. Perhaps in long-term treatment of hypertension, a reduction in the incidence of stroke is easy to judge, but there are so many grey areas and I really do not have an easy answer.

X. Carné: I think there's another example that I always like to remember. From 1970s to 1990s, classical non-steroidal anti-inflammatory drugs came into the market with, in my opinion, very few information on dose equipotency among them. We were working on that field, and many other groups found, though different epidemiological studies, that the risk of upper gastro-intestinal bleeding was slightly different among those drugs. Probably because it's a dose-depending adverse effect common to all the group, and we have to know that they were marketed at different dose-equipotent levels. After many years and many studies, what happens now on this field? In the year 2000, ibuprofen is on the market all over the world, and in many countries as an OTC drug. On the other side, pyroxicam in many studies has shown higher risk of upper gastro-intestinal bleeding in marketed doses in those countries, it's not an OTC, and it's just a not-very-used drug. So in my opinion, that is an example to the crucial role of comparative studies among drugs of the same drug class because otherwise the market will decide which drug is going or not to be used at the end.

P. Joubert: I agree with you. We need a paradigm change. We clinical pharmacologists tend to look for PD markers of efficacy, and even if we are including comparators in early studies, we look at efficacy comparisons, but often not at the therapeutic index comparison. These comparisons in terms of risk–benefit will sort themselves out on the market if you do not do it while you are doing the development. I cannot resist referring back to something mentioned this morning. I saw tolcapone going into man, getting to the market as an anti-Parkinsonian agent with clear labelling to monitor liver function tests. It was a very good example of what happens out in the real world, where a small number of physicians used the drug probably without adequate monitoring for hepatotoxicity that led to deaths that practically killed the drug. Your phase III control setting does not represent what happens out there in the real world, and you can label as much as you want for a safety hazard. If there's a significant safety hazard you cannot label away, the problem will happen.

N. Holford: We've heard about some new aspects of science, predicting first dose in humans, some fancy measurement techniques and mathematical modelling, but only Pieter Joubert talked about optimisation. In the most trivial case, of the two examples he gave, the best dose for ritonavir was actually the lowest dose, so it wasn't clear whether it was optimum, and for carvedilol, the best dose was the biggest dose, so that wasn't clear whether it was optimum either. I think this group should perhaps try and discuss a little bit how do you optimise the dose, rather than talking about the extreme doses, and about the bits of science that might help to do that. How do you measure good effects against bad effects when they are measured in different scales?

P. Joubert: I touched on it very briefly, but in essence it boils down to get the best risk–benefit ratio. You are dealing on the one hand with the commercial drive to have standardised therapy for the standard patient, and on the other end of the scale, the need for individualisation of therapy. The only way you can really optimise therapy is by individualised treatment because of the variability in kinetics and dynamics, unless you have a drug with an extremely wide therapeutic index where you just push everybody onto the plateau—but there are not many of them around. One of the areas that is going to force us into this is the genetic push, which is one of the things that I have inherited within our group. We have been interested in the bimodal distributions of polymorphisms, but the responses that are unimodally distributed, in fact, probably represent many subpopulations. We might eventually enter an area of individualisation of dosage based on genetic background and monitoring end points.

G. Levy: I think the concept of dose optimisation as a one-step process is bound to fail because it neglects the fact that there are two major sources of variability: the pharmacokinetic and the pharmacodynamic. Then, the first step has to define the appropriate concentration of unbound drug in most cases, and then one has to go to the next step to pharmacokinetics, and rely on population PK/PD to see if in fact it's rational to offer one adult dose strength rather than several. The other point is about phase IV; Lewis Sheiner raised the question but didn't get an answer in the discussion. We have to rely more and more on phase IV studies, recognising the limitations in information we currently gain in phases I, II, III. These phases have a well-defined structure, imposed upon us mainly by regulatory agencies. Phase IV does not have a structure except in the rare instances where regulatory agencies require it, and most of the time there has been no follow-up. So the question I pose is, is there a need for some sort of structure for phase IV follow-up, and what should that be?

M. Reidenberg: I wanted to address this because we keep looking as if the total responsibility for this is by the sponsor of a particular drug and yet the groups that have the most phase IV data are those with organised medical practices, for example, in the United States it is some of the HMOs. We have used epidemiological techniques with this sort of data almost exclusively for adverse drug reaction monitoring. What would be useful, in my opinion, is to start to develop a conceptual means of getting valid information on comparative therapeutic efficacy using epidemiological techniques. There is a wealth of data on drug use in practice in these databases and much of it is already in digital or retrievable form. The next step, seems to me, is to take some of these epidemiological methodologies that we use for adverse effects and drug toxicity and try it to evolve a way to get the additional data that we are looking for in a valid scientific manner.

L. Sheiner: Both Marcus and Gary have been asking: what should we do formally in phase IV? One suggestion is to recognise that phase IV is a learning phase, not a testing phase. A second suggestion is to decide what are the data elements that we need to have in order to be able to draw conclusions from phase IV data with reasonable certainty (not great certainty—that is not possible with non-randomised designs), and to be sure to gather these in a systematic fashion. Indeed, just measuring relevant variables on a regular basis gets rid of much of the confounding that bedevils causal inference with observational data. To stress a point I've often made before, we so rarely think about doing data analyses other than from a hypothesis testing point of view, which we do not address the design

issues associated with analyses that are more learning-oriented. The way to go here is to get the best data one can, but not to the point where the best is the enemy of the good, where one puts such constraints on the practice of medicine that people will not gather the data, or they will start to lie about what they do. For example, I have been associated with studies where nurses are required to fill in the exact time of dosage, or of blood drawing. They make it up because it's too much of a burden to get it exactly right. It's much better to record "unknown", or a range, e.g. between 9:00 AM and 11:30 AM. Such data are more useful than "ten fifteen exactly", which is usually nonsense.

To address for a moment Nick's point, optimisation is a two-edged sword. Obviously, you want to optimise while pay-off is significantly increasing, but the problem is that medical pay-offs are very difficult to measure. If we increased the benefits derived from any billion-dollar drug by 1%, for example, there would be a huge public health pay-off, but we have no way of tracking such small increments in benefit, even though, when multiplied across a huge population, they can make a real difference to our public health budget. So one of our problems is that optimisation may not appear worthwhile, if the only things we can see are gross shifts in the number of people who die, or the amount of money we spend. Indeed, the amount of money we spend on drugs or health care is so poorly correlated with health outcomes that it's a bit difficult to imagine that we could use even that. If I'm right, then there is a fundamental problem here: we've got to act on faith, rather than on proof, that optimisation beyond obvious gains is still worth doing, but I return to an earlier question of mine: what are we doing right? How is it that what amounts to a vast post-approval uncontrolled trial by physicians all over the world does get the dose right? Or if not right, then a lot righter than when the dose comes out of an extremely expensive, highly formal developmental process? What then can we do in phase IV to make the information we gather a little bit better so we can learn better and faster than we do with this "natural process?"

N. Holford: Well, the simple answer why it's right is that trial and error is very good at getting the right answer, eventually and all we're talking about is can we make it happen faster? A grid search is a great way of finding the right estimates, but there are more efficient methods, faster methods. The only thing that we are interested in here is speed. Now, the other dimension that we can measure is money. Pharmacoeconomics is one way to try and bring apples and oranges together. I would say our drug development programs, in a clinical pharmacology sense, largely ignore pharmacoeconomics. That is the other dimension that we ignore at our peril in designing and making decisions about in early drug development, rather than phase IV issues, where I think money comes into it much more.

A. Bye: I think every drug industry has got its department of pharmacoeconomics, but I don't know whether they use it in the right way. It's usually about smashing the opposition rather than optimising the dose of drugs. I think what's being raised now is the wider debate. I just wonder whether optimisation is the emerging issue and I know that certainly within our own company, what we are doing is formally running a small number of patient studies, after the classic registration to address this issue. These types of studies are not imposed on us by the regulatory authorities. They explore new treatment paradigms, and it's becoming more common and accepted, but it's been a tough job to persuade the late-phase clinical community to sample in the way you would sample an investigative clinical pharmacology study. However, I think that in most places that's pretty well accomplished

now, it's not seen as the exciting end of the business, and I think there was a huge expectation that the PK/PD could be done so early, almost that cartoon that I drew for you 'just put the money up front and somehow that takes care of the downstream events'. It's just clearly untrue. I mean that you've got to invest downstream as well, and I think every industry is finding that.

M.M. Reidenberg: I'll just raise the ideas really first articulated by B.B. Brodie, with respect to small organic molecules that act reversibly. If one looks at the products of biotechnology (peptides, antibodies), it's been my impression that there hasn't yet been a theoretical or conceptual development for how to look at these issues of dose optimisation for the macromolecular drugs. From some that I've seen, the development of these drugs has often been pretty amateurish, compared to what we can do today with small organic molecules and if some of the touted benefits of this whole biotechnology revolution are really going to be realised at the bedside, then I think that we need to develop a conceptual framework to address dosage and development of these compounds better than simply to let us try something and see what happens. That has been done in the past, and we have advanced very far from the days of B.B. Brodie and what he actually articulated.

X. Carné: I just would like to add that interferon could also be a very good example of looking for the optimum dose in many diseases in a phase IV way.

K. Park: A comment on dose optimisation, the therapy for safety and why I said to look for a dose that was safe, rather to optimise for a safe dose. I think with type A reactions that's quite straightforward, but the point about type B reactions is that they don't show simple dose-dependency, that's one problem, for those people who can model these things. The other thing is that these usually take weeks, and sometimes months to occur. It's beyond the pharmacokinetic modelling of accumulation of drug and the metabolites. How do we explain that on a model? Do we think in terms of daily dose, cumulative dose (as you do with chloroquine), so there are other ways of looking at optimum dose: we have to look in terms of total chemical stress.

A. Bye: Just to sum up, I think we've seen the presentations so far have started to open up to two major holes in the knowledge base. First, predicting the toxicology or the unwanted effects, and really trying to use that to better optimise dose in a prospective PK/PD approach. Secondly, we do have to do much more in the phase IV. I think that they are the two areas we need to think much harder about and bring back. There is a lot of the symposium yet to run, so I think these are the two key questions that have come out in my mind as needing further debate.

References

- [1] A.C. Collier, R.W. Coombs, D.A. Schoenfeld, et al., Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine, *N. Engl. J. Med.* 334 (1996) 1011–1017.
- [2] R. Gieschke, B. Fotteler, N. Buss, J.-L. Steimer, Relationship between exposure to saquinavir monotherapy and antiviral response in HIV-positive patients, *Clin. Pharmacokinet.* 37 (1999) 75–86.
- [3] K. Jorga, N. Buss, Pharmacokinetic drug interaction with saquinavir soft gelatin capsule, 39th Inter-science Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 26–29 September 1999, American Society for Microbiology, Abstract 0339.

- [4] J.M. Kilby, G. Sfakianos, N. Gizzi, et al., Safety and pharmacokinetics of once-daily regimens of soft-gel capsule saquinavir plus minidose ritonavir in human immunodeficiency virus-negative adults, *Antimicrob. Agents Chemother.* 44 (2000) 2672–2678.
- [5] R. Paredes, T. Puig, A. Arno, High dose saquinavir plus ritonavir: long term efficacy in HIV-positive protease inhibitor-experienced patients and predictors of virologic response, *J. Acquired Immune Defic. Syndr.* 22 (1999) 132–138.
- [6] R.C. Parish, R.J. Miller, Adverse events of angiotensin converting enzyme (ACE) inhibitors, *Drug Saf.* 7 (1992) 14–31.
- [7] C.H. Kleinbloesem, P. Van Brummelen, M. Danhof, et al., Rate of increase in the plasma concentration of nifedipine as a major determinant of its haemodynamic effects in humans, *Clin. Pharmacol. Ther.* 41 (1987) 26–30.
- [8] E.J. Lewis, L.G. Hunsicker, R.P. Bain, R.D. Rohde, The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy, *N. Engl. J. Med.* 329 (1993) 1456–1462.
- [9] M.R. Bristow, Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blockers, *Am. J. Cardiol.* 71 (1993) 12C–22C.
- [10] M.R. Bristow, E.M. Gilbert, W.T. Abraham, et al., Congestive cardiac failure/myocardial disease: carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure, *Circulation* 94 (1996) 2807–2816.
- [11] T. Pullar, A.J. Birtwell, P.G. Wiles, et al., Use of a pharmacologic indicator to compare compliance with tablets prescribed to be taken once, twice or three times daily, *Clin. Pharmacol. Ther.* 5 (1988) 540–545.
- [12] M. Gibaldi, Failure to comply: a therapeutic dilemma and the balance of clinical trials, *J. Clin. Pharmacol.* 36 (1996) 674–682.