Variability in Human Drug Response
G.T. Tucker, Editor

Variable patient compliance as a source of variability in drug response

John Urquhart

Pharmaco-epidemiology Group, Maastricht University, Maastricht, The Netherlands

ABSTRACT

Patient compliance varies widely, but with what effect on drugs' actions?... beyond the obvious fact that drugs can't work when patients don't take them. Electronic monitoring shows that one-, several-, or many-day lapses in dosing are, in that order, the most common forms of noncompliance. How rapidly drug action fades during a multi-day lapse in dosing is usually not studied, but a slow off-response can allow drug action to persist during shorter lapses. On-responses, usually studied, often do not predict off-responses: some drugs with fast onset of action have slow off-responses, and vice-versa. Thus experimental data on off-responses are needed. Other factors that lessen the impact of shorter dosing lapses are: (a) zero-slope portions of hyperbolic concentration-effect (C-E) relations; (b) intermittent flattening of the entire C-E relation with some types of long-acting drugs. Either way, C can vary within a flat segment of the C-E relation without effect on E. Within limits, these nonlinear mechanisms contribute to the reliability of some drugs' responses, despite variability in dosage form functionality, compliance, and/or PK.

Key words: patient compliance, variability in drug response, pharmacodynamics, concentration-effect relations, rebound effects, first-dose effects.

Correspondence: John Urquhart, M.D., 975 Hamilton Avenue, Palo Alto, California 94301, USA, Tel: +1-650-321-3961, Fax: +1-650-324-9739, Email: urquhart@ix.netcom.com

INTRODUCTION

Variable patient compliance is a leading source of variability in drug response. This fact is reflected in the Harter-Peck (H-P) model of the sources of variability in drug response [1], which is a landmark in the analysis of variability in drug response and its sources. H-P used ^{9}theophylline to illustrate the main sources of variability and the mathematics that describe how each source contributes to overall variability in drug response when all components have linear kinetics or dynamics. The model is an informative starting point for analyzing drugs with more typically nonlinear pharmacodynamics (PD), which create a rather different situation than the all-linear case of the H-P model. The need to understand the clinical

implications of the common patterns of noncompliant dosing, particularly the multiday lapse in dosing (the "drug holiday"), has put new light on some of the nonlinearities in PD, especially those that determine the persistence of drug actions during lapses in dosing.

The H-P model presents pharmacokinetics (PK) and patient noncompliance with prescribed drug regimens as the two greatest sources of quantitative variability in drug response. Since the H-P model was formulated, much has been learned about both PK and patient compliance. The latter is the focus of this paper. Electronic medication event monitoring (EM) and reliable chemical marker methods have revealed the spectrum of variable drug exposure due to poor and partial compliance, and EM has shown the variety of temporal patterns of drug exposure that occur and recur in ambulatory patients [2-4].

DEFINING THE CLINICAL CONSEQUENCES OF COMMON LAPSES IN DOSING

The need to know the clinical impact of lapses in dosing has exposed a frequently missing element in clinical drug development: few drugs come to market with data on how long drug action persists when dosing is interrupted. The time course of a drug's actions after dosing halts is conveniently referred to as the drug's "off-response". In contrast, most drugs have a well- characterized time-course of action as dosing begins, conveniently referred to as the drug's "on-response". Many drugs have a well-described response to a single dose, which is an amalgam of on- and off-responses, but the duration of response to a single dose rarely allows time for the body to develop full counter-regulatory responses to the drug's actions. Counter-regulatory responses can play a dominant role in off-responses, but are not a prominent topic in pharmacology, which often ignores the fact that drugs act within a rich meshwork of homeostatic, physiological feedback mechanisms.

A further consequence of the need to understand the clinical impact of lapses in dosing is a relatively new clinical study design: the controlled substitution of placebos for active drug. First used with oral contraceptives, as reviewed in [5], this design has recently been applied to anti-hypertensive agents [6-9], and to selective serotonin reuptake inhibitor (SSRI) antidepressants [10]. Of course, in many conditions the controlled placebo-substitution is too hazardous to impose on trial volunteers. Then one must make do with observational data on the clinical correlates of dosing lapses as they occur on the patient's own initiative.

Why have off-responses been neglected in clinical development? One reason is that it has only been in the past decade that EM has shown that dosing lapses are too common and too big to ignore. Previously, off-responses had been seen as one-time events that occurred when the prescriber ordered the drug's discontinuation. Another factor has been perseveration in linear thinking carried over from PK to PD, bringing the linear assumption that on- and off-responses are symmetrical, mirror images of each other. Examples of major asymmetries make it imprudent to assume dynamic symmetry in on- and off-responses. PK/PD models could be seriously unreliable when unconstrained by actual data from off-responses.

Three key points arise out of the foregoing considerations:

(a) Off-responses, which are basic to understanding the impact of the most common patterns of noncompliant dosing, must be determined experimentally; they are not reliably predicted from on-responses.

(b) Certain pharmacodynamic nonlinearities create *qualitative* as well as quantitative variability in the response to variations in drug exposure, especially to the holiday pattern, which recurs sufficiently frequently (see below) to complicate trials analyses.
(c) Certain other PD nonlinearities may beneficially attenuate the propagation of variability that arises from drug formulations, compliance, or PK.

These three points and their implications are the main topics of this paper. Their practical relevance follows from the fact that variability in drug response is the inverse of reliability in use, which is a key value-parameter for any product.

Before we consider these three points, it is useful to review the main points of the H-P model and its assumption that variable compliance is a leading source of variability in drug response.

BRIEF REVIEW OF THE HARTER-PECK MODEL

The H-P model has four components, serially arrayed, each with its own variability, represented with a coefficient of variation (CV, standard deviation as a percentage of the mean), the magnitudes of which Harter and Peck estimated from available data and educated guesses. The serially-arrayed components, through which drug passes from packaged dosage form to receptor-initiated drug action, are: drug formulation, compliance, PK, and lastly, PD.

COMPONENT	ESTIMATED CV(%)	SQUARED CV	TRANSFORMATION
drug formulation	20	400	drug quantity into release rate
compliance	50	2500	prescribed intake into actual intake
PK	50	2500	release rate into concentration(s)
PD	30	900	concentration(s) into effect(s)
	SUM OF SQUARES	6300	
	OVERALL CV	79%	

In the linear H-P model, the CV for the overall response is the square root of the sum of the squares of the CVs of the individual components, as tabulated above. The column entitled "transformation" denotes the changes in physical dimensions effected by each component. "Concentration(s)" are those of drug and/or active metabolites in plasma or other apt fluid.

SOME IMPLICATIONS OF THE H-P MODEL

H-P constrained their model by the estimate that patients' responses to a dose of theophylline intended to give a half-maximal response have a CV of 80%. Such variability is akin to an elevator in a 20-story building that is likely to go to any floor when "10" is

pressed, which would promptly terminate its use, until repaired. Theophylline continues in clinical use, but its unreliability is one of the factors that has limited its use.

PD is the final process in the serial structure of the H-P model. Thus, PD can, depending upon the shape of the concentration-effect relation, amplify or attenuate quantitative variability arising from the first three processes, as Levy has noted [11]. One means of attenuation arises from the familiar hyperbolic dose-response relation, which can be approximated by three segments:

i. a zero-slope segment at concentrations too low to elicit any drug action
ii. a finite-slope segment in a mid-range of concentrations
iii. an essentially zero-slope segment at concentrations greater than needed for maximal action.

In reality the slope in segment iii may not be literally zero, but close thereto; the approximation as zero is convenient for this discussion. As a result, drug concentrations can vary within segments i or iii and make little or no change in the magnitude of drug action characteristic of the respective segment, i.e., zero within segment i, or essentially maximal action within segment iii. This functional characteristic is important in limiting the propagation of variability arising from drug formulation, compliance, or PK. In contrast, the slope of segment ii not only passes variability but may even amplify it: with a very steep slope in segment ii, a small percentage fluctuation in drug concentration can swing response between zero and maximum.

A limiting case is provided by drugs that have so-called "hit and run" actions, e.g., omeprazole and reserpine, which can totally inactivate, by irreversible binding, a key component of the mechanism upon which the drug acts. Omeprazole, e.g., irreversibly binds to the H+/K+ ATPase that is responsible for gastric acid secretion; once bound to drug, this enzyme ceases to function, and 3-5 days are required for new enzyme to be synthesized [12]. Thus, while omeprazole's on-response is fully developed within about an hour, its action continues for 3-5 days, signifying that the slope of segment ii is reduced essentially to zero. As a result, variations arising from drug formulation, compliance, and PK have little or no effect during the long off-response [13]. These long periods of attenuated propagation of variability contribute to omeprazole's high degree of reliability in use, which is reflected in the strength of its therapeutic claims [12]. Of course, some drugs achieve long action from their PK, not their PD, and can be represented by familiar linear mechanisms that create frequency-dependent attenuation of variability [14].

The H-P assumption that variable patient compliance plays a leading role in the variability of drug response makes compliance a topic to reconsider now, especially as the model was published shortly after EM methods for measuring compliance were introduced. In the intervening decade, many studies based on EM methods have been published, showing various patterns of variable drug exposure, some of which can trigger qualitative as well as quantitative variability in drug response.

THE COMMONLY OCCURRING PATTERNS OF NONCOMPLIANT DOSING BY UNSELECTED AMBULATORY PATIENTS

The methods used to gather these data are reviewed elsewhere [3]; key points are summarized here. EM and slow-turnover marker methods make it very difficult for patients to censor evidence for delayed or omitted doses, in contrast to older methods, which allow easy censoring: returned tablet counts, interviews, histories, diaries, and spot checks of drug concentration in plasma, all of which overestimate compliance [3], often grossly so [15].

Marker and EM methods are complementary: markers prove ingestion of drug, and give a measure of aggregate intake of drug, but cannot show when doses were taken; EM shows when doses were taken and thus the temporal patterns of drug exposure, but cannot prove ingestion, which has turned out not to be a substantive limitation. Thus, the simpler and lower-cost EM methods have become the standard for reliable assessments of drug exposure in clinical research. A recent cost-reduction makes EM practical for distinguishing pharmacological non-responders from noncompliers in various practice settings. For pharmacometric studies, the time-history of drug intake, which only EM can provide, is crucial for defining the effects of variable compliance on drug response.

DEFINING COMPLIANCE

EM data support a precise definition of compliance: the extent to which the patient's actual drug dosing history corresponds to the prescribed drug regimen [3].

What compliance is not: the three phases of ambulatory pharmaco-therapy

Ambulatory pharmaco-therapy has three distinct phases, of which compliance, as defined, applies to the second phase.

The first phase is the patient's acceptance of the concept of treatment and agreement to execute the prescribed regimen. Patients naturally have the right to reject the proffered treatment, but some do it covertly by not having the prescription filled, or by not collecting or not starting to take dispensed medicine. Prescribers who fail to recognize non-acceptance are likely to interpret the ensuing non-response as drug-refractory disease, which can be a costly error.

The second phase, applicable to those who start treatment, is execution of the prescribed regimen. It is an ongoing process, with opportunities for errors of both omission and commission, whence the definition of compliance given above. It is in this phase that various temporal patterns of drug intake contribute to dose-dependent fluctuating magnitudes of drug responses, and, in some circumstances, pattern-dependent, qualitatively different drug responses.

The third phase is discontinuation of treatment, which may occur on medical advice or on the patient's own initiative. Either way, early discontinuation of treatment is a common occurrence. It is much in need of study, as recommended durations of treatment are often not met. Early discontinuation may bring avoidable hazard to the patient, and has several kinds of economic impact.

One could, of course, lump both non-starting and early discontinuation as "noncompliance", but it mixes up two usually one-time events with the ongoing process of

regimen execution. It seems preferable to use "adherence" as the blanket term covering all three phases, of which the first and third - adoption and continuation - are dichotomous, usually one-time occurrences; the second - drug regimen compliance - encompasses a spectrum of often recurrent deviations from the prescribed dosing regimen.

DOSING PATTERNS DEFINED BY ELECTRONIC MONITORING

EM data define subgroups of patients according to dosing patterns, including some subgroups likely to enrich the understanding of the drug's exposure-dependent actions, e.g., --

- About a third of unselected patients have full, unrelenting exposure to drug, and thus can be expected to show full effects of the drug, both beneficial and adverse.
- Another third of unselected patients have recurring drug holidays and thus reveal potentially hazardous effects of sudden stopping or restarting of dosing; holidays recur ca. monthly in half these patients, and ca. quarterly in the other half, as reviewed in [3].
- The remaining third of unselected patients take appreciably less drug than called-for by the recommended regimen, though without lapses in dosing long enough to be classed as holidays; their responses constitute a "reality check" on whether the recommended dosing regimen calls for needlessly frequent or high doses.

"Unselected" means that the patients' prior medical history has not been such as to selected for unusually good or poor compliance, a topic discussed in [3].

The drug holiday -- key source of mischief

EM reveals drug holidays, defined as three or more days of interrupted dosing [16], during which drug actions fade and eventually disappear, if dosing is halted long enough, but then resume after dosing resumes. This is the quantitative aspect of variability in drug response created by drug holidays.

Qualitative variability arises because drug holidays also serve as the trigger for rebound or acute withdrawal effects, which differ qualitatively from the drug's usual actions. Rebound effects appear in the days following a sudden halt in dosing, following a period of more or less well-maintained dosing. Some rebound effects are hazardous, as discussed below. Resumption of dosing may also trigger recurrent first-dose effects, which also differ qualitatively from primary effects [3].

KEY PHARMACODYNAMIC POINTS

A. Off-responses not predictable from on-responses

Several currently best-selling pharmaceuticals illustrate this point. Already described are the asymmetrical on- and off-responses of omeprazole, the drug with largest-ever sales. One might caricature its on- and off-responses as "fast-on, slow-off". In contrast, the opposite pattern - "slow-on, fast-off" - prevails for the SSRI antidepressant, paroxetine, also a leading

product. Like other anti-depressants, paroxetine takes 10 days or more of dosing before any anti-depressant action is evident, and a further week or so before anti-depressant action is fully developed; in contrast, when paroxetine dosing suddenly halts, mood deteriorates within 2-3 days [10]. Thus, on- and off-responses can be markedly asymmetrical in either direction, making it essential that both on- and off-responses be studied experimentally. Without such data, assumptions about off-responses are too unreliable to project the clinical impact of the common lapses in dosing. Simulation of clinical trials and computer-assisted trials design may be similarly unreliable when based on PD models unconstrained by experimental data on off-responses.

Off-responses determine the parameter called "forgiveness", defined as the drug's post-dose duration of therapeutically useful action (D_a) minus the recommended dosing interval [3]. Long-acting drugs can forgive occasional lapses in dosing that do not exceed the drug's D_a. In practical terms, a drug that can forgive the occasional occurrence of two sequentially omitted doses will make variable compliance a non-issue in 70-80% of patients. In contrast, a drug with only a few hours of forgiveness can be expected to have recurring lapses of action in a majority of patients, with likely negative impact on treatment outcome [13,17].

B. Qualitative variations in drug responses due to variable dosing

A well-recognized form of qualitative variability in drug response arises from the familiar concept that the most desirable drugs have dose-dependent beneficial effects occurring at relatively low doses, with side-effects occurring at considerably higher levels of dosing. By keeping the dose in the proper range, only the desired, therapeutic effects of the drug are elicited; in the face of variability in PK, it may be necessary to adjust the dosing level to stay within a desired range of drug concentrations in plasma to achieve selective action. In some instances, however, the trigger for undesirable side-effects is not the amount of drug taken, or the concentration of drug in plasma, but sudden stops or starts in dosing.

Examples of rebound effects

The two best-known rebound effects are the withdrawal syndrome that occurs when long-maintained dosing with a narcotic analgesic is suddenly discontinued, and the coronary spasm, hypertension, tachycardia, and increased risk of incident coronary disease that occur when a sudden halt occurs in long-maintained dosing of beta receptor antagonists of the non-ISA category. Rangno and Langlois [18] showed how the response to exogenous isoproterenol changes in the days following cessation of beta blocker dosing: the initially small response, characteristic of receptor blockade, is reversed within several days to a level of response far higher than that which prevailed prior to the start of beta blocker treatment. Then gradually, over a 10-14 day period, response returns to the pre-treatment baseline. These changes signify changes in receptor sensitivity, a counter-regulatory response to receptor blockade that is revealed during the off-response because the beta blocker disappears and beta blockade fades much sooner than hyper-responsiveness to catecholamines. The drug's off-response is an amalgam of the two processes. During periods of catecholamine hyper-responsiveness, the patient runs a gauntlet of elevated risk of incident coronary disease and/or coronary spasm [19,20].

Recurrent first-dose effects - likely examples

Many drugs have prominent first-dose effects [3], but their recurrence when dosing resumes after drug holidays has not yet been studied.

Overview

The holiday pattern of drug dosing can trigger rebound effects and probably also recurrent first dose effects that differ qualitatively from the drug's usual effects. Some of these pattern-dependent effects are hazardous, but the safety problems are obscured by intention-to-treat analysis, which ignores drug exposure, and simply averages qualitatively diverse data from all randomized patients. The result is an underestimate of risk in those patients who are actually at risk, and a misattribution of diluted risk to the majority who are not at risk.

C. CERTAIN NONLINEARITIES IN PD CAN ATTENUATE THE PROPAGATION OF VARIABILITY

The means by which the PD of omeprazole can attenuate variability have already been discussed. Another example is reserpine, which, along with hydralazine, was used in the VA Cooperative Trial that first demonstrated the value of treating hypertension [21,22]. Reserpine has about a two-week D_a, so, with its once-daily dose, it is extremely forgiving, which arises, as with omeprazole, from its nonlinear PD; there are many-day intervals in which the drug's concentration-effect relation is completely flat, and thus unable to propagate variability originating from drug formulation, compliance, or PK. It is also noteworthy that the compliance of patients in the VA trial had been screened, pre-randomization, by a marker method that probably served to exclude from the study non-acceptors and the worst of the poor compliers. In summary, several extra-ordinary aspects of this trial had the effect of markedly attenuating variability that usually prevails in trials of other types of drugs, at the cost of statistical power.

The results of the VA Cooperative Trial have been a landmark in the hypertension field, which has been subsequently beset by many ambiguous trial results with agents whose forgiveness is measured in hours, not days. There are doubtless multiple reasons for the singular clarity of the VA Cooperative Trial results, but clarity can only have been enhanced by use of an extremely forgiving agent and exclusion of non-acceptors and patients whose compliance was too poor to be offset even by the extreme forgiveness of reserpine. These qualitative considerations of course need to be translated into quantitative terms, which could be done by retrospective simulation of this and other trials, focused on the sources of variability in drug response. Indeed, it would seem that meta-analysis of complicated fields like hypertension can be enriched by retrospective computer simulations of key trials. A principal objective of this kind of "dynamic meta-analysis" would be an examination of the role of differential degrees of forgiveness and how their associated attenuation of variability may have influenced trial outcomes.

CONCLUSION

Variability in drug response is the inverse of reliability in use, which is a key value-parameter for any product, pharmaceuticals included: reliability is a powerful competitive advantage. Accurately differentiating noncompliance from nonresponse as the basis for poor outcomes of treatment is a basic step, and has been done in the oral contraceptive field since its beginnings. Best is to understand the sources of variability in drug response and to design drug formulations, regimens, and individualized dosing schemes that maximize forgiveness, minimize variability, and minimize the propagation of variability. As Sir David Cox recently noted [23], variable patient compliance, as we now understand it, has major implications for design and statistical analysis of drug trials, with, of course, strong echoes in practical therapeutics.

ACKNOWLEDGEMENTS: The author has had useful discussions on key points in this paper with Carl C. Peck, Lewis B. Sheiner, and Gerhard Levy.

REFERENCES

1. Harter JG, Peck CC. Chronobiology: suggestions for integrating it into drug development. Ann NY Acad Sci 1991;618:563-571.
2. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. Drugs 1995;49:321-327.
3. Kastrissios H, Blaschke TF. Medication compliance as a feature in drug development. Ann Rev Pharmacol Toxicol 1997;37:451-475.
4. Urquhart J. The electronic medication event monitor - lessons for pharmacotherapy. Clin Pharmacokinet 1997;32:345-356.
5. Guillebaud J. Any questions. Brit Med J 1993;307:617.
6. Johnson BF, Whelton A. A study design for comparing the effects of missing daily doses of antihypertensive drugs. Am J Ther 1994;1:260-264.
7. Vaur L, Dutrey-Dupagne C, Boussac J. Differential effects of a missed dose of trandolapril and enalapril on blood pressure control in hypertensive patients. J Cardiovasc Pharmacol 1995;26:127-131.
8. Leenen FHH, Fourney A, Notman G, Tanner J. Persistence of anti-hypertensive effect after 'missed doses' of calcium antagonist with long (amlodipine) vs short (diltiazem) elimination half-life. Br J Clin Pharmacol 1996;41,83-88.
9. Hernandez-Hernandez R, Armas de Hernandez MJ, Armas-Padilla MC, Carvajal AR, Guerrero-Pajuelo J. The effects of missing a dose of enalapril versus amlodipine on ambulatory blood pressure. Blood Pressure Monitoring 1996;1:1121-1126.
10. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998;44:77-87.
11. Levy G. A pharmacokinetic perspective on medicament noncompliance. Clin Pharmacol Ther 1993;54:242-244.
12. PRILOSEC (omeprazole). In: Physicians' Desk Reference. Montvale (NJ): Medical Economics Co., 1998;528-532.

13. Urquhart J. Pharmacodynamics of variable patient compliance: implications for pharmaceutical value. Adv Drug Delivery Revs (in press).
14. Yates FE, Brennan RD, Urquhart J. Application of control systems theory to physiology. Adrenal glucocorticoid control system. Fed Proc 1969;28:71-83.
15. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? Clin Pharmacol Ther 1989;46:163-8.
16. Urquhart J, Chevalley C. Impact of unrecognized dosing errors on the cost and effectiveness of pharmaceuticals. Drug Inform J 1998;22:363-378.
17. Urquhart J. Can drug delivery systems deliver value in the new pharmaceutical marketplace? Brit J Clin Pharmacol 1997;44:413-419.
18. Rangno RE, Langlois S. Comparison of withdrawal phenomena after propranolol, metoprolol, and pindolol. Am Heart J 1982;104:473-478.
19. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta blockers. JAMA 1990;263:1653-1657.
20. Anon. Long-term use of beta blockers: the need for sustained compliance. WHO Drug Information 1990;4:52-53.
21. Veterans Administration Cooperative Study Group on Hypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. JAMA 1967;202:1028-1034.
22. Veterans Administration Cooperative Study Group on Hypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970;213,1143-1152.
23. Cox D. Discussion: Limburg Compliance Symposium. Stat Med 1998;17:387-389.

Discussion: Variable patient compliance as a source of variability in drug response

M. Lader:

I was involved in writing for a patient group recently and the person who ran this group said I must not use the word "compliance", I must use the word "concordance". Have you encountered this opinion?

J. Urquhart:

Some see in the term 'compliance' an authoritarian doctor-patient relationship, but 'compliance' is the term under which published papers in this field are indexed by the Index Medicus, regardless of the term used by the authors, e.g. adherence. The document you cite [Marinker M, (for the Working Party). From compliance to concordance: achieving shared goals in medicine taking. London: Royal Pharmaceutical Society, 1997], emphasized patient 'empowerment' as a means to help patients achieve satisfactory treatment. This theory is challenged by the prevalence of poor compliance among physicians who self-prescribe. As my paper notes, ambulatory pharmacotherapy has a beginning (acceptance) a middle (drug regiment execution), and an end discontinuation of the treatment regimen). For successful treatment, the patient has to accept, execute, and then at the proper time, discontinue treatment. Treatment can fail at any phase, so "adherence" can be a useful blanket term, with "nonadherence" implying non-acceptance, early discontinuation, or poor execution of the prescribed regimen. To study, however, the pharmacometric consequences of actual dosing patterns, we need a defined parameter for deviations of actual from prescribed dosing patterns. For that, 'compliance with the prescribed drug regimen' is apt. If 'concordance' adds anything but novelty, it escapes me.

L. Aarons:

I would like to ask you to comment a bit more about the quality of electronic monitoring data, from the perspective that what is being measured is the removal of the lid, or whatever, of the bottle.

J. Urquhart:

Certainly a patient intent on creating a false dosing record can open and close the containers, and not take the medicine. But he has to do it on schedule because everything is time-stamped and it is not possible to change the timing. If people manipulate the package and do not take the medicine, then the data are worse than I have shown you, not better. Occasionally an issue with electronic monitoring of is oral dosage forms arises with patients who are set on using a dose organiser. They do not want to use one of these cup-type packages for one drug in their multi-drug regimen. If you have a patient who is adamant about using an organizer, my suggestion is to let him do so and classify him or her *a priori* as a full complier. Some day there will be an electronically monitored multi-dose organiser. With eye-drop medicines, the monitor records time and date when you take the cap off and turn the bottle upside down. That again is difficult to falsify. The people who have worked with the method are convinced that it is a substantially reliable measurement of exposure and the best currently available. If you try so to use chemical marker methods, you encounter problems with pharmacokinetic variance. One of the best methods is Morgan Feely's phenobarbitone method, which is

surprisingly good considering that from a single measurement on 1 day you can obtain a reliable aggregate view of drug intake over the last 10-14 days. But it does not tell you when doses were taken, and I think the timing information is really the critical finding, because of drug holidays. If you look at the drug holiday from a pharmacometric point of view, it is quite worrying because it opens up a whole new set of adverse reaction possibilities.

I.P. Hall:

I was wondering if you had any data on what the effects of electronic drug monitoring are on compliance. Despite having some sort of electronic monitoring, people could say they are taking the medication when they are not.

J. Urquhart:

Joyce Cramer has looked at this by randomising patients between being informed and not being informed (Cramer JA *et at.*, Epilepsia, 1990) and found no difference. In general, if you do not stress the issue, whether patients are informed or not does not have any discernible effect. A very striking point is soon to be published by Hans Brunner's hypertension group in Lausanne. They have studied patients who have gone through the four-step care scheme with no response to multiple doses and drugs, and then have been sent to the University Clinic for a work-up for drug resistant hypertension, which means renal angiograms, and pheocromocytoma tests, etc. Initially, the patients are put on a basic thiazide plus β-blocker regimen for 60 days with electronic monitoring, and explained in detail the procedure and the reasons for this study. In the first 32 patients, 14 of them returned with a record of good compliance and were normo-tensive for the first time in a whole series of treatment strategies. This is a powerful step forward in this field, and I think we will see more cases like this. To return to the step-care scheme, if, for example step 1 to step 2 consists of a change of a 20 cents a day treatment cost to a 2 $ treatment cost, it is worth spending 15 cents a day for approximately a month to see whether the patients are taking their medication. If you can keep a few people at the 20 cent a day level and not have to pay the 2 $, it makes economic sense. However, it is only over the last 2 years that this approach has now become practical.

I.P. Hall:

I suppose that electronic drug monitoring works well for diseases where you have got a clearly defined end-point. It is less good in the field I work in, asthma, where you are largely dependent upon patients' subjective reporting of symptoms, unless you believe all their peak flow records, which is subject to the same problem as medication recording is.

J. Urquhart:

Some problems with anti-depressant treatment should also be considered. For example, what happens when drug dosing suddenly stops. About a year ago, Lilly sponsored a study in which they randomised people between sertraline, paroxetine, and fluoxetine, treated them for about 8 or 10 weeks, and then did a placebo substitution for 7 days. There was a very striking clinical deterioration in the paroxetine group, the drug that has the shortest half-life of the three. Whether it was caused by rebound effects or just return of the depression is not clear. This deterioration was a hitherto unknown aspect of that mode of treatment, and it is in a grey area where it is hard to make measurements. Nevertheless, one can still see that these problems.

N. Benowitz:

In those drugs with not very good efficacy, compliance may not be an important issue. But there may be toxicity, for example in the case of non-steroidal anti-inflammatory drugs. Are there studies about the relationship between compliance and drug toxicity, independently of efficacy?

J. Urquhart:

I mentioned there was just some sort of hit-or-miss issues. For example, in an hypertension trial there was a patient who after a week of taking isradipine according to the schedule, suddenly took six doses within a relatively short time and then took nothing for the next week. He decided to stop the treatment because of a terrible reaction of nausea, dizziness and feeling bad. But when one sees those patterns of underdosing not always there is some drug-related reason, because you can also see the same patterns when you look at placebo compliance. The thing that drives the regimen execution goes back to the kinds of routines people have in their lives. If they are in a chronic dosing situation and they have reasonably good routines, they can fix the dosing behaviour so that it is triggered by some recurring routine in your life (tooth-brushing, walking the dog, watering the plants, etc.). Then you will be a pretty good complier as long as things do not fall apart. I have a stockbroker in New York who has glaucoma, and he said to me at one point his big problem was taking his midday dose. I said to him, well, what do you do at lunch? And he said well my wife packs a paper bag with a couple of sandwiches. I said, next time you get your prescription filled, get a couple of extra bottles of the medicine and have her pack the medicine in the lunch bag so when you dump your lunch out, there is the medicine and then you can take it. He was thunderstruck by the originality of the notion that you would have more than one medicine container. And a couple of months later he said: it really works. I have solved the problem, except on the occasional day when the market is really crazy and then he never gets around to opening the lunch bag, so he does not get the medicine, but that does not happen very often. So I think, when you look at those patterns, and if you have in your mind's eye the slide I showed with similar compliance patterns in three very disparate disease conditions, it suggests that those are not responses to treatment situations so much as they are reflections of the way people organise their lives.

If you have an individual patient without very good routines in their life, then you have to question what is best to do. If the treatment requires punctuality for continuity of drug action in order to get a therapeutic benefit, and if interruptions in drug action are hazardous, then I do not think you should give the patient the medicine. There are some circumstances where drug actions are such as to modulate dosing behaviour. If your patient receives a bolus dose of furosemide every morning, the brisk diuresis that ensues prevent his doing anything else in the next several hours. Perhaps he is taking four or five other medicines, he may take those but decide to delay the diuretic. A deferred dose is outside the normal routine and is a dose more likely to be missed, which can risk the problem of salt and water accumulation.

C. Martínez:

Would you conclude that if you do real-life studies and look at compliance, that we would get an under-estimate of the risk of drugs?

J. Urquhart:
Yes. Let's take the case of the selective COX-2 inhibitors. If you are going to do a clinical programme, you want to be able to show your selective COX-2 inhibitors devoid of the usual kind of gastrointestinal side-effects. That question is answerable in about one third of the people you bring in a randomised controlled trial, without some kind of compliance selection, because it is only in a third of the patients you are going to have unrelenting exposure. There is another hypothesis that another third tests: What is the effect of off-again on-again dosing? It may be with GI bleeding, which is still mysterious, that on and off dosing may be some kind of a special trigger. Maybe not. But there is one way to tell, there is a natural experiment going on out there all the time that you can look at, but you have to do the compliance monitoring to know which patients are doing it and when. And then while it is an observational study, subject to biases and so on, there is one nice check in this, which is, that causality flows downhill in time, it only goes in one direction. If you see the drug holiday and then you see the problem, that is a nice temporal association. But it means you have got to time the occurrence of clinical events correctly, and that is not always the easiest thing to do.

C. Martínez:
But in general, we could then say that the type A reactions, those that are dose-dependent, would be under-estimated?.

J. Urquhart:
If you say unrelenting exposure is needed to elicit this particular adverse effect, and you have three thirds of your patients, in only one third of whom there is unrelenting exposure, then you under-estimate by a factor of three. But underestimating risk by a factor of three is not a major sin.

C. Martínez:
If you take GI bleeds, it is a lot.

J. Urquhart:
It depends who you listen to. If you get excited about these little tiny relative risk differences, then it does matter. But I have another rule of thumb, called the rule of fives, which is if the relative risk is not bigger than five or if it is not one of the top five causes of death, I just do not pay any attention to it.

C. Martínez:
Then you did not listen to my presentation.

G.T. Tucker:
I just wondered whether we could recognise a non-compliant phenotype, or even a gene for non-compliance, perhaps?

J. Urquhart:
The behaviourists have looked for predictors, but nobody has found reliable methods to measure personality traits of compliance. In countries where doctors as a routine do home visits, they get a very much clearer view.

D.A. Smith:
Does it make sense to reduce the number of pills, and are combination products helpful in improving compliance?

J. Urquhart:
One issue is the number of pills you take at a time, and the other is how many doses a day. The number of doses per day issue is up in the air at the moment. Pretty much everybody who has looked at it has seen that if you just look at the percentage of prescribed doses taken, you get a little higher percentage with a once-a-day than you do with a twice-a-day regimen. But it is a small difference. But then, if you start looking at the timing, there are some studies that indicate that, with once-a-day dosing, you tend to get more egregiously long lapses in dosing with the once-a-day than with twice. It may happen that, from a marketing point of view, we must have a once-a-day product, because otherwise we cannot sell it, and the formulators go and torture the product until they squeak it past the 24th hour. Then you put a very unforgiving product in the market. That is fine, but if you then depend on outcome studies to sell the product in the long run, you are going to lose, because if you put an unforgiving product in the market, you are going to get poor outcomes later, because you are going to have that many more gaps in treatment; if continuity of drug action is essential for good outcome, then you are not going to get good outcomes.

D.A. Smith:
I was specifically not asking on once-a-day or twice-a-day. If you took a β-blocker and a diuretic, it is two pills, and you replaced it with a combination in one pill, does that aid compliance?

J. Urquhart:
Joyce Cramer looked at this in a big epilepsy study (Cramer JA *et al.*, Epilepsia, 1995) where people took one, two, three, up to four different medicines synchronously. Basically, if they take one, they take them all, almost invariably.

M. Reidenberg:
A couple of decades ago, the group at McMaster's (Haynes RB, *et al.* In Sackett DL, eds. Compliance in Health Care, Baltimore, Johns Hopkins U. Press, 1979) claimed that what would influence compliance was the patient's knowledge of the severity of the illness and the degree of efficacy of the treatment.

J. Urquhart:
Never did there come from that group a strong voice for reliable measurement. All those measurements were based on methods in which the patient could easily censor evidence for omitted doses, and when you have methods like that, you are doomed. I think most of the conclusions drawn were specious. I think that what we have in hand now is we have got methodology that allows you to do real management.

M. Reidenberg:
Their outcome measure was fall in blood pressure in patients with hypertension.

J. Urquhart:
Using the drug response as an end-point is a difficult and awkward manoeuvre. What we should look at is the dosing record, what I call management methods and I think it is the best we have.

M. Kinirons:
Can you comment on the role of educational aids to assist in the initiation? I have this perception that if you spend some time with a patient and you give them some leaflet, you aid in compliance. Is that true or false?

J. Urquhart:
Information and compliance are qualitatively very different. For securing the patient's acceptance of treatment, you need all the help you can get, for you have to convince the patient in some way or another that the disease is real and that there are real methods of treatment. In day to day execution of the regimen, however, information does not, *per se* compete well with priority in a busy schedule. So advanced knowledge about drugs and their mechanisms of action and the rationale for their use does not guarantee punctual execution of the drug regimen.

E.M. Sellers:
A variety of sociologic studies would suggest that along some social value axes and health belief axes, women are different from men. For example, about 35% of women state a much higher degree of risk aversion than do men. I am wondering, with respect to health behaviours around compliance, whether there is any data that would suggest that there are differences between men and women either on average, or whether there are sub-groups of individuals. The sociologic data would predict that the perception of adverse reactions, or perhaps even the actual occurrence of them, might have greater saliency in women. Is there any evidence to support this at all?

J. Urquhart:
The risk aversion and the question of adverse reactions relates more to discontinuation than it does to a daily debate about whether to take the medicine. As far as the execution issue goes, the person who is done more of this than anyone else is Joyce Cramer at Yale. She just throws up her hands and says, there is nothing that you can look at. The only predictor of compliance is compliance. In other words, if you have measured it in the patient, it is a good predictor of what is going to happen subsequently. But male/female, old/young people, it all tends to come out about the same, with such a wide range of values that do not mean anything.