COMMENTARY

Clin Pharmacokinet 2006; 45 (1): 105-108
0312-5963/06/0001-0105/$39.95/0



# 'Hedged' Prescribing for Partially Compliant Patients

The term 'hedge' has multiple meanings; its use here is analogous to its meaning in financial markets, i.e. 'to protect oneself from losing or failing by a counterbalancing action'.[1] The paper by Blesius et al.[2] strives to achieve a therapeutically useful degree of 'counterbalancing action' in the prescribing of oral anticoagulants by switching between either of two available drugs and/or between once- and twice-daily dosing. Their approach deserves attention and consideration for extension into other fields of ambulatory pharmacotherapy as a risk-management tool.

Blesius et al.[2] do not suggest the term 'hedging' but the several manoeuvres that one could employ to achieve useful counterbalancing action against omitted doses probably warrant a specific term, which we propose to be 'hedging'.

Let us consider prescription hedging manoeuvres in a broad context and then examine some of the details.

## 1. Overdosing: the Simplest but Least Satisfactory Hedging Manoeuvre

A simple but inherently unsatisfactory hedge against delayed and omitted doses, i.e. partial compliance, is to prescribe a substantially higher dose than needed for full efficacy with the prescribed dosing regimen, punctually executed. The actions triggered by a higher dose will take longer to dwindle to ineffective levels during longer-than-prescribed intervals between doses. Part of this effect is pharmacokinetic, in that it takes longer for a high concentration than a low concentration of drug in plasma to fall to levels incapable of sustaining therapeutic drug action. Many drugs, however, have actions whose durations substantially exceed what one would predict from their pharmacokinetics alone (see Urquhart[3]); therefore, the emphasis is on dwindling action, subsuming both pharmacokinetics and pharmacodynamics.

An informative example of shifting between high and low doses was provided by the major reduction in steroid doses in the combined estrogen-progestogen oral contraceptive products after 1970, when the risk of thromboembolic problems became evident with the original, high-dose products. The dose reduction substantially reduced thromboembolic risk, but at the cost of reducing the duration of steroidal blockade of ovulation, after a last administered dose. The older, high-dose products had provided at least 2 days of continuing steroidal blockade after the last administered dose,[4] thus providing considerable 'forgiveness' for occasional omissions of one or even two scheduled doses. Following the introduction of the lower-dose products, a sudden increase of unplanned conceptions indicated that the dose reductions had shrunk the margin for errors of omission.

During the 1980s, five studies were conducted in which placebo 'pills' were substituted, in a suitably blinded and controlled manner, for active 'pills'. The studies were largely done with volunteers selected from women who had earlier undergone tubal ligation, rendering them sterile but still having normal hormonal dynamics of ovulation. The studies, referenced and summarised by Guillebaud,[5] served as the basis for relabelling the low-dose oral contraceptives with a new section, under the heading "What to do if you miss a dose". The UK drug labelling indicates that the risk of 'breakthrough' ovulation begins to rise after the 36th hour since the last administered dose, i.e. 12 hours since the missed dose should have been taken, and advises that the missed oral contraceptive pill should be taken as soon as the error has been discovered, with ongoing daily dose administration, coupled with the use of barrier contraceptives for the succeeding 7 days, to allow adequate time for restoration of the steroidal blockade of ovulation.

The tactics for 'catching up' after omission of one, two, or more of the low-dose oral contraceptive 'pills' are summarised in the drug labelling, as discussed by Guillebaud.[5] The US drug labelling is less stringent than the UK drug labelling as it advises that no special action needs to be taken unless more than 48 hours have elapsed since the last administered pill. Details of the tactical manoeuvres recommended to compensate for omitted doses are given in the US labelling for these products.[6]

Thus, in the steroidal contraception arena, the original hedging manoeuvre of relative overdosing was replaced by a set of instructions for patients to follow when a lapse in dosing occurs and is discovered. How much help these instructions provide in practice is not clear. Whenever patients are asked to execute a special manoeuvre, the question perforce arises of how well their execution of the manoeuvre corresponds to the instructions.

A useful overview of the effectiveness of steroidal contraceptives is provided in table I.

The 50-fold increase in conception rates between 'perfect' and 'typical' use of the low-dose, combined estrogen-progestogen oral contraceptive is a striking example of the need for pharmionic assessment in understanding the failure-modes of ambulatory-use medicines – pharmionics being the discipline concerned with how patients use medicines.[8] As table I also indicates, the ultimate hedging manoeuvre is automatic administration of drug by an implant, with the patient's involvement being only to return for a replacement at scheduled intervals (5 years in the case of NORPLANT®).[1] As shown in table I and by other methods of maintaining continuity of drug exposure,[9] strictly maintained continuity of exposure of a variety of drugs has proved capable of providing almost full efficacy in virtually all patients. Although promising, experience on this point is limited to a few drugs available as depot injections or implants. Such results with these delivery methods require drugs whose pharmacodynamics are not subject to tachyphylaxis. Other aspects of the implant approach are discussed by Urquhart.[9]

**Table I.** Annual conception rates among women using either the once-daily oral, combined estrogen-progestogen contraceptive 'pill', at two Centers for Disease Control-defined levels of quality of use, or the 5-year duration subcutaneous implant of levonorgestrel[7]

| Method | Perfect use (%) | Typical use (%) |
|---|---|---|
| 5-year implant (NORPLANT®) | 0.05 | 0.05 |
| Daily 'pill' | 0.1 | 5.0 |

## 2. What can be done to Provide Useful Hedging with the Typical Drug that is Administered Orally, Once- or Twice-Daily?

Blesius et al.[2] considered a variety of simulated dosing histories, deciding between two drugs (warfarin or acenocoumarol) given once- or twice-daily. In other words, the choice of drug and dosing frequency are the hedging manoeuvres.

While simulation is often a good starting point to form initial views on what might be possible, definitive simulations should be done with real data on real patients' dosing histories, from a dataset large enough to provide not only a comprehensive inventory of dosing errors, but also reliable estimates of their probabilities of occurrence and recurrence. Another aspect of 'large-enough' dataset should be determined by what is needed for confident projection of the impact of various hedging manoeuvres on risk levels of major hazards, e.g. stroke or major bleeding in the case of oral anticoagulation.

The pharmacological differences between the two drugs are relatively modest, as is the simulated effect of switching between drugs. In contrast, the simulated effect of switching between once- and twice-daily dosing frequency is large, with the advantage lying strongly with the twice-daily regimen.

The superiority of twice-daily over once-daily dosing, across three of the four patterns of dosing history, with either drug, flies in the face of long-running propaganda about the superiority 'for better compliance' of once-daily dosing.

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

## 3. Why does Twice-Daily Dosing Provide Hedging Superior to that of Once-Daily Dosing?

Countless studies show that the percentages of prescribed doses taken are virtually always modestly higher with once-daily than with twice-daily dosing. The clinically important question, however, is not how many pills are or are not taken, but how well maintained is the therapeutic action of the drug in question under the two regimens. The therapeutic action of oral anticoagulation has a clear-cut measure, expressed in the international normalised ratio (INR) level. Thus, Blesius et al.[2] projected the aggregate times when the INR level would be too low, or too high, in the face of various dosing patterns, as given in their table III. The superiority of the twice-daily regimens for both warfarin and acenocoumarol is clearly reflected in the finding, in all dosing patterns except pattern number 2, of less time spent with either too low or too high INR levels. Moreover, use of the twice-daily regimen for pattern 2 was certainly no worse than what was attained with the once-daily regimen.

The resolution of the apparent paradox lies in the metric one uses to express patient compliance. The usual metric is 'percentage of prescribed doses taken'; usual because that is the only measure of drug use that pre-electronic methods can provide. Electronic monitoring, as Blesius et al.[2] point out, reveals the patient's time-history of dosing, from which interdose interval data can be derived. It is the lengths of interdose intervals, rather than percentages of prescribed doses taken, that appear to contain most of the clinical explanatory power of drug dosing history data.[10]

As Vrijens et al.[11] have recently shown with data from a large archive of electronically compiled drug dosing histories, the crucial factor in the comparison between once-daily and twice-daily regimens lies in the fact that two to three sequential omissions of doses are needed with the twice-daily regimen in order to produce a fall in the plasma concentration of drug equivalent to what is produced by the omission of a single once-daily dose. In either regimen, the probability of sequentially omitting two to three doses is considerably lower than the probability of omitting a single dose. Missing a single dose in the twice-daily regimen has minor consequences, in contrast to the major consequence of missing a single once-daily dose. Therefore, the origin of the twice-daily advantage arises from the substantially lower probability of occurrence, in the twice-daily than in the once-daily dosing regimen, of dosing errors of equivalent therapeutic impact. The relatively high incidence of single, missed doses is the crucial factor in making a shift from once- to twice-daily dosing a useful hedging manoeuvre. It is not a trivial matter, as omitting a single dose is the most common dosing error that ambulatory patients commit. Obviously the clinical consequences will vary with drug and disease. The findings by Vrijens et al.[11] echo earlier work by Levy[12] and Kruse et al.[13]

## 4. Do Not Overlook Persistence

The story will not be complete until patients' comparative persistence with once- and twice-daily regimens of prescribed drug use is also studied. Is the convenience difference between the two regimens large enough to create a differential in persistence with one regimen versus the other? Inconvenience is of course amplified by ancillary instructions regarding dose-timing in relation to meals or the administration of other drugs. Thus, answers to the comparative persistence question may depend on the totality of patients' programmes of prescribed drug intake.

## 5. Pharmionic Questions Need Comprehensive Answers

It is time to put comparisons of drug dosing regimens on a sound scientific footing that includes the temporal aspects of drug doses administered – whence the need for the discipline called pharmionics. It is also time for the terminology used in this field to reflect both administration and timing of doses, to jettison pill counts and to focus on pharmacometric consequences of various dosing patterns so as to understand how they may undermine effectiveness or increase risk. Simulation stud-

ies can be very useful, but should be based on actual dosing histories that include dose-timing information from real patients, prescribed real pharmaceuticals, for real diseases. The study by Blesius et al.[2] is a good start.

*John Urquhart*[1,2] and *Bernard Vrijens*[1,3]

1 AARDEX Ltd, Zug, Switzerland

2 Department of Biopharmaceutical Sciences, Center for Drug Development Science, University of California at San Francisco, San Francisco, California, USA

3 Department of Biostatistics and Medical Informatics, University of Liège, Liège, Belgium

## References

1. Merriam-Webster's Collegiate Dictionary, 10th ed. Springfield (MA): Merriam-Webster, Inc., 2001
2. Blesius A, Chabaud S, Cucherat M, et al. Compliance-guided therapy: a new insight into the potential role of clinical pharmacologists. Clin Pharmacokinet 2005; 45 (1): 95-104
3. Urquhart J. Variable compliance and persistence with prescribed drug dosing regimens: implications for benefits, risks, and economics of pharmacotherapy. In: Strom B, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley, 2005: 767-89
4. Potter LS. Oral contraceptive compliance and its role in the effectiveness of the method. In: Cramer JA, Spilker B, editors. Compliance in medical practice and clinical trials. New York: Raven Press, 1991: 195-207
5. Guillebaud J. Any questions. BMJ 1993; 307: 617
6. "What to do if you miss pills"? In: Physicians' desk reference. 59th ed. Montvale (NJ): Medical Economics Co.: 2541
7. Ten great public health achievements US, 1900-99: family planning. MMWR 1999; 48: 1073-80
8. Urquhart J. The odds of the three nons when an aptly prescribed medicine isn't working: noncompliance, nonabsorption, nonresponse. Brit J Clin Pharmacol 2002; 54: 212-20
9. Urquhart J. Controlled drug delivery: pharmacologic and therapeutic aspects. J Internal Med 2000; 248: 357-76
10. Vrijens B, Gross R, Urquhart J. The odds that clinically unrecognized poor or partial adherence confuses population pharmacokinetic/pharmacodynamic analyses. Basic Clin Pharmacol Toxicol 2005; 96: 225-7
11. Vrijens B, Comte L, Tousset E, et al. Once-daily versus twice-daily regimens: which is best for HIV-infected patients [abstract no. 3; poster no. 1.3]. 6th International Workshop on Clinical Pharmacology of HIV Therapy. 2005 Apr 28-30. Quebec City (QC)
12. Levy G. A pharmacokinetic perspective on medicament noncompliance. Clin Pharmacol Ther 1993; 54: 242-4
13. Kruse W, Rampmaier J, Ullrich G, et al. Patterns of drug compliance with medication to be taken once and twice daily assessed by continuous electronic monitoring in primary care. Int J Clin Pharmacol Ther 1994; 32: 452-7