For debate

Variable patient compliance in ambulatory trials—nuisance, threat, opportunity

John Urquhart

Department of Epidemiology, University of Limburg, 6200 MD Maastricht, The Netherlands, and APREX Corporation 47221 Fremont Blvd, Fremont, CA 94538, USA

Introduction

Hippocrates observed that many patients failed to take prescribed medicines but were not averse to blaming the physician if their condition deteriorated. Medicines have since improved, but perversity persists: poor compliance with immune suppressants, a leading reason for rejection of transplanted organs, is a case in point (Didlake et al., 1988; Rovelli et al., 1989).

Dosing of most drugs, including antimicrobials, is an act of faith, and benefits may not be immediately perceived; in the case of prophylactic agents, it may be impossible to assess the relationship between dose and outcome. For most drugs, underdosing is the main compliance error. Compliance has also been overestimated in clinical trials (Pullar et al., 1989; Rudd et al., 1989). Most physicians acknowledge that compliance is often a problem, though they may deny it in their own patients. Poor methods for assessing compliance have perpetuated these uncertainties.

Since 1986–7 two new methods have gained acceptance as generally reliable measures of compliance. These open the way to realization of the opportunities suggested by the title of this article.

New methods for assessing drug compliance

The methods have been reviewed (Pullar & Feely, 1990; Bond & Hussar, 1991), but are summarized here. One involves labelling of drugs with an inactive, low-dose chemical marker such as digoxin (Mäenpää et al., 1987; Mäenpää, Manninen & Heinonen, 1987) or phenobarbitone (Feely et al., 1987); the latter has had widest usage (Pullar & Feely, 1990). In the other new method, time-recording microcircuitry, is inserted into various types of drug packaging and time and date of removal of the drug are recorded by means of microswitches or optical sensors when a package is opened and closed, or, in
some designs, when a dose is removed (Kass et al., 1986b; Eisen et al., 1987; Cheung et al., 1988; Cramer et al., 1989; Potter 1991; Tashkin et al., 1991).

Both methods measure drug exposure. The chemical methods prove ingestion of drug within a certain period of time, but tell nothing of dose timing, or of dosing outside the time period. For example phenobarbitone in blood confirms ingestion of a drug between 2 and 6 days previously (Feely et al., 1987). Electronic methods record times when doses are removed from their packs, and are capable of recording continuously for months, but they cannot prove ingestion. Some electronically monitored packages are designed to record the number of dosages removed (Eisen et al., 1987; Cheung et al., 1988; Potter, 1991), but such complexity seems rarely necessary. Each method has been reasonably validated by observation (Averbuch, Weintraub & Pollack, 1990), serum monitoring (Rubio, Cox & Weintraub, 1992), and clinical assessment (Cramer et al., 1989; Kruse & Weber, 1990; Olivieri et al., 1992). Both confirm that underdosing is common, involving a third or more of patients. Overdosing is usually not an issue (Vander Stichele, 1991; Kruse, 1992).

Strict compliance is exceptional. For example, in a group of 112 Swiss patients prescribed a once-daily antihypertensive, only one patient in six took all doses and maintained dosing intervals within 24 ± 6 h throughout a 1 month period (Heynen, G, personal communication). Others have also found that once-daily dosing does not ensure compliance (Pullar et al., 1988; Cramer et al., 1989; Kruse et al., 1991), and may exaggerate adverse effects of missed doses (Anonymous, 1991).

Errors in dose timing are common, though most are trivial. A drug requiring critical dose timing would probably fail to satisfy regulatory authorities and so drugs for non-hospitalized patients must allow for some degree of 'forgiveness', in the sense of being able to maintain action despite an occasionally omitted dose (Urquhart, 1990). Drugs of the same class vary in their ability to forgive common dosing errors (Johnson, Whelton & McMahon, 1990), a new concept that only a few drug developers have begun to quantify. All else being equal, the most successful drug in a class will be most forgiving of common compliance errors.

Partial compliance (usually defined as taking 40–80% of prescribed doses) is reported in at least one third of patients (Urquhart, 1991a). Most partial compliers improve their compliance in the day or two before a medical appointment, (Kass et al., 1986a; Cramer, Scheyer & Mattson, 1990), behaviour described as 'white-coat compliance' (Feinstein, 1990). Poor compliance may not be recognized since 1–2 days of correct dosing brings plasma levels of most drugs into the therapeutic range. Thus it may be hard to recognize poor or partial compliance clinically (Kass et al., 1986a).

One in about five patients makes occasional but repeated interruptions in dosing, so called drug 'holidays'. First discovered in sight-threatened glaucoma patients (Kass et al., 1986b, 1987), drug holidays occur in many fields of therapy (Vander Stichele, 1991; Kruse, 1992) including treatment of infectious diseases (Drehobl et al., 1991; Paladino et al., 1991; Geletko et al., 1992) and so the clinical consequences are diverse (Uurquhart & Chevalley, 1988). It has long been recognized that inadequate treatment with antimicrobials favours the emergence of resistant organisms, and multiply drug-resistant tuberculosis is probably a consequence of poor compliance (Bloom & Murray, 1992; Lederberg, Shope & Oaks, 1992). Now that lapses in compliance are measurable, much more information about the impact of 'holidays' is potentially available.

Many infectious diseases need only short-term treatment, but medication is often discontinued prematurely; although there may be no serious consequences for individuals with mild infections, the possibility of promoting bacterial resistance remains.
Variable patient compliance

Natural experiments in dose-ranging

Ordinary variations in compliance during fixed-dose trials create natural experiments in dose-ranging, and offer useful opportunities for study. Three examples illustrate this statement.

1. **Poorest compliers as 'virtual placebo'**. Long ago, Feinstein and colleagues assessed three regimens for preventing streptococcal infections and recurrent rheumatic fever in a 5-year randomized study of 471 patients (Gavrin, et al., 1964; Wood et al., 1964a,b). They compared monthly injections of depot penicillin with once-daily oral penicillin G and also with once-daily oral sulphadiazine. A placebo group was ethically impossible. Only half the patients taking oral therapy complied, though 94% of the injection group had good compliance because of vigorous follow-up. This appears to have been the first account of a 'virtual placebo' group — certainly not as reliable as a true placebo, but not without some value and relevance to clinical assessments.

There are several reasons for caution in assessing poor compliers as a 'virtual placebo' group — some drugs are exceptionally forgiving, with fair or good results even when compliance is poor (Johnson et al., 1990; Kruse et al., 1991; Paladino et al., 1991). In Feinstein's studies the rates of streptococcal infection were equally high in poor compliers with both oral regimens; inexplicably the rate of recurrent rheumatic fever was as low among poor compliers with sulphadiazine as among good compliers with either oral agent, a discovery that challenged accepted concepts.

2. **How long need treatment continue?** Drehobl et al. (1991) compared two oral cephalosporins in lower respiratory tract infections in a multicentre study of 115 patients treated for 14 days. All treatment failures occurred in patients who dosed for less than 6 days, as recorded by electronic compliance monitors. Nearly half the successfully-treated patients were partial compliers. Thus, a successful outcome required neither strict compliance, nor the full 14 days of treatment as recommended; one week appeared to be enough. A randomized controlled trial could assess the validity of such a conclusion.

3. **Why treatment fails.** Geletko et al. (1992) electronically monitored dosing in a study of thrice-weekly fluconazole for prophylaxis of recurrent candidiasis in women with AIDS. On average, the patients took two of three prescribed doses. Four of five episodes of breakthrough candidiasis were preceded by periods of interrupted dosing.

When treatment fails, it may be difficult to distinguish between noncompliers and nonresponders. Analysis of dosing patterns in the days before breakthrough episodes may indicate errors likely to dispose to reinfection — information that could provide a basis for educating doctors and patients about avoidable problems. Johnson et al. (1990) studied the consequences of dosing lapses in a controlled trial, when such trials cannot be undertaken for ethical reasons, inferences must be drawn from natural experiments (Goldstein & Goldstein, 1978; Sheiner, 1991).

Natural variations in dosing in ambulatory patients have only occasionally been turned to advantage to explore dose-dependent activity of drugs. (Rubin, 1991; Urquhart, 1991b; Zeger & Liang, 1991). If dosing lapses are ignored, as in intention-to-treat analysis (Meier, 1991; Newell, 1992), assessment of drug responses may be considerably distorted (Efron & Feldman, 1991; Sheiner, 1991).

Ascertaining the best dose

Choice of the best dosing regimen during drug development is always difficult and often wrong, usually erring on the high side (Temple, 1989). One way to avoid this mistake is
to correlate compliance with drug efficacy in pre-market trials. Exceptional forgiveness suggests that the dose has been set too high; doses of an exceptionally unforgiving drug may be set too low, or dosing intervals too long. Setting acceptable margins of forgiveness is a research challenge, but will lead the way to designing drug regimens on the basis of real data rather than assumptions about patients' actual dosing.

Some will worry that forgiveness implies overdosing of good compliers. Two points must be considered. Firstly, common dosing errors with forgiving drugs are probably less likely to permit emergence of resistant organisms. Secondly, concerns about overdosing might better be focused on body size in adults, as with children. The usual practice of giving the same dose to all adults, irrespective of size implies over- or under-dosing of some patients.

Is poor compliance avoidable?

Reliable measurements suggest two new approaches. The concept of forgiveness indicates a pharmaceutical basis for minimizing the impact of some of the commonest dosing errors; further data on the limits of forgiveness should add credibility to dosing information for both doctors and patients. The recognition of 'white-coat compliance' reveals that the vast majority of patients comply properly when they feel accountable for correct dosing. Sustained accountability for correct dosing should be a new element in the doctor-patient relationship. Work has just begun using recorded dosing histories to introduce sustained accountability into medication management. Until now, patient accountability for compliance with dosing instructions has been lacking, as physicians have had to rely on patients' own accounts, an unsound basis for effective management and probably an important reason for the mixed results obtained in patient counselling programmes (Haynes et al., 1976; Inui, Yourtee & Williamson, 1976; Bond & Monson, 1984; Gerson et al., 1992).

Some believe that patient education is the answer. Ignorance doubtless contributes to poor compliance, but education which requires time and resources, is not a panacea. My enquiries amongst health professionals about their own compliance indicates that technical knowledge does not compete effectively for priority in a busy schedule.

Conclusion

Variable compliance by ambulatory patients in fixed-dose trials creates natural experiments in dose-ranging. Natural experiments must be interpreted cautiously, but relating dosing patterns to treatment outcomes can identify dosage regimens that are sub-optimal, and point to drug regimens that can forgive some of the more common errors in dosing.

Multi-day holidays from dosing and shortened courses are frequent dosing errors that are now quantifiable, which should make it possible to assess their roles in the emergence of resistant microorganisms.

References

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