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Commentary

How Much Compliance Is Enough?

Until recently, the title's question had been researched with randomized, controlled trials in only one field of medicine. Studies from 1979-86 provided answers in that field, recently translated into labeling in the United Kingdom (1). It informs patients that if they are >12h late in taking their once-daily tablet, they should take the missed tablet, continue once-daily dosing, but take precautionary measures to prevent treatment failure for the next 7 days. Additional instructions concern bigger errors. So, here is the answer in one field to the question "How much compliance is enough?".

It happens to be in the field with the highest cumulative drug exposure — oral contraception. It warrants some consideration, being the only field in which the title's question has been posed, answered, and put into labeling.

There are many details. American regulators have interpreted the trials more loosely, and "allowed" the patient to go past the 48th hour after the last-taken dose before starting precautionary measures, which are use of barrier contraceptives for 7 days (2). When more than 2 successive doses have been skipped, patients are told to discard the pill-pack, to use barrier methods until the next menses, and then start a new pill-pack. Some complain about wasting pills, but a partly-used pill-pack is a degraded informational sequence; like a bad floppy disk, it can too easily create costly problems.

DOES ALL THIS REALLY MATTER?

Indeed. Correctly-used oral contraceptives provide complete contraception, but the tolerance for error is small and the consequences costly. Understanding is facilitated by a lucid distinction: method-effectiveness and use-effectiveness. The former defines how well oral contraceptives work when used correctly; the latter, how well oral contraceptives work in particular groups of patients, with their particular mix of compliance. Contraception rates with correct use are near zero; rates in sexually active non-contraceptors are 60–85 per hundred women years, and rates among different groups of women using the oral contraceptives range from about 1 to as high as 20 per hundred women years (2,3). A unique aspect of this field is that various groups of women have differing proportions of full, partial, and non-compliance (3).

There are many unanswered questions, but oral contraceptives have the quadruple virtues of (a) a solid endocrine basis of understanding, (b) essentially complete method-effectiveness, (c) long recognition of substantial differences in compliance among various groups of users, and (d) a pragmatic fusion of clinical and biostatistical thinking. On (d), only those bereft of common sense could conceive of averaging data from sexually adventurous teenagers and married mothers of two.

DIFFERENT PRODUCTS HAVE DIFFERENT ANSWERS

"How much compliance is enough?" has also been asked of the progestin-only oral contraceptives. With these, the risk of conception rises after the 27th post-dose hour (4), making even greater demands for the uncommon virtue of consistent punctuality. Yet the same steroid, formulated as a 5-year implant, has the highest level of use-effectiveness of any non-surgical method of contraception (5).

ROLE OF DOSE

Dose can modify the answer to the title's question. The original oral contraceptives had high estrogen doses, allowing patients to skip several days' doses with little risk of breakthrough ovulation and conception (3). Estrogen dose was reduced, however, when the thrombo-embolic problems of the high-dose products became evident. The low-dose products appear to avoid thrombo-embolic problems, but have only a 12-24h margin for error in dose timing (3).

OTHER FIELDS

What do we know about other fields of medicine? Not much, but a hopeful sign is the recent comparison of two once-daily beta blockers in their ability to maintain action after substitution of a placebo for the usual daily dose (6): atenolol lost its pressure-lowering action after hour 30, but betaxolol maintained action at least to hour 48, indicating that an occasional omission of one dose of betaxolol would not entail loss of blood pressure control.

To my knowledge this is the first use outside the field of contraception of randomized, controlled trials to answer the title's question. There have been, of course, observational approaches (see 7), but where ethically and technically possible the question is best answered with randomized, controlled trials.

The differences between the two once-daily beta blocker products opens a new form of marketing differentiation of otherwise similar products: forgiveness for the more common lapses in dosing. These differences are seen in the 30-40% of patients who occasionally delay or omit doses; differences will not be evident in the majority who dose correctly or in the small minority who take few or no doses at all. The target group is thus the 'partial compliers'—a large enough minority to be a market opportunity in their own right.

TAKE-HOME LESSONS

Lesson One: The answer to 'How much compliance is enough?' is product-specific. An old, still widely-held idea, going back at least as far as the Coronary Drug Project Trial in the 1960's (see 7), was that taking 80% of the prescribed

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doses qualifies, across-the-board, as satisfactory compliance. This view is pharmacodynamically naive, however.

Lesson Two: Post-dose duration of drug action (Da) is a key parameter in determining how much compliance is enough (8,9); the size of Da relative to the prescribed interval between doses (Ip) determines how much latitude the patient has in delaying the next dose. Pharmacokinetic considerations alone will sometimes greatly underestimate Da (9,10).

One might suppose that the ratio Da/Ip, which defines "forgiveness", is also a parameter of pharmaceutical value, relating as it necessarily must, to the product's reliability in use.

Lesson Three: High doses extend duration of action, but may be hazardous; delivery systems, when feasible, are the better approach.

Lesson Four: Like-indicated products can differ greatly in duration of action, creating a basis for claiming superior forgiveness, with its direct bearing on outcomes in a world well-populated by partial compliers.

Lesson Five: Once-daily products with a duration little longer than 24h will require a degree of punctuality in remedication that only a minority of patients maintain—a recipe for poor outcomes.

ONCE-A-DAY DOSING: NOT NECESSARILY BEST

Once-daily dosing has been oversold (11), so Lesson Five needs careful attention—particularly with the growing focus on outcomes. But outcomes take time to assess, so what to do in the interim? Everyone wants the best outcomes from drug treatment, physicians and formulary committees alike, but the latter are probably better able to see beyond slogans to assess the determinants of outcomes.

In comparing similarly-acting agents, the key point is not differences in compliance, for the distributions of compliance outside the field of contraception are remarkably similar from drug to drug and field to field (12-15). The key difference is the degree of forgiveness for the most common errors in compliance. A noteworthy finding (16) is a higher occurrence of multiday lapses with once-daily than with twice-daily regimens, even though a greater percentage of prescribed doses were omitted with the twice-daily regimen. It is a product-specific issue whether one long lapse causes more problems than the equivalent in many brief lapses.

OVERVIEW

Studies with reliable compliance assessment have shown that the main error patients make is to take the prescribed dose at longer-than-prescribed intervals—often by hours, sometimes by days, occasionally by weeks (15). Shorter lapses can be offset by designing a degree of forgiveness into the product, but that approach has its limits, so the longer lapses will necessarily interrupt the actions of even the most forgiving products. Another problem created by dosing lapses is the occurrence of hazardous rebound effects with some drugs—a topic newly reanimated (17) as we now see the time-patterns of dosing.

It's timely for drug developers to abandon the "once-daily's best" sloganeering and address the question posed by the title.

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