Therapeutic implications of drug ‘holidays’

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While a patient may appear to be fully compliant with respect to quantity of medication ingested, the timing of doses can vary considerably. This may introduce protracted intervals between doses, particularly if dosing frequency is greater than once daily. This commonly presents in the form of drug holidays, where dosing is omitted for 1 or more days, followed by a resumption of full-strength dosing, possibly resulting in excessive drug effects when dosing suddenly resumes, rebound effects when dosing is suddenly stopped and a period without effective drug action. Poor compliance has not only been associated with poorer treatment outcome, but also with financial consequences. It has been suggested that hospitalization due to non-compliance accounts for 11-7% of all healthcare expenditure in the U.S.A.

Differences between drugs, in terms of both their concentration-time profiles and their duration of action, will lead to some agents being more effective than others in the face of interruptions in dosage. A drug with an intrinsically long duration of action, such as the calcium antagonist amlodipine, will provide better therapeutic coverage than those with a shorter duration of action and therefore minimize effects generated by an intermittent pattern of dosing.

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Introduction

It has long been recognized that patients often do not wholly follow the instructions for the use of their medication. For most diseases there is no ‘one-shot’ physician-administered therapy. Drug treatment must, therefore, rely heavily on the cooperation of the patient for self administration and the term ‘compliance’ has been used to describe how well the patient adheres to a recommended dosage regimen. Despite a recognition by prescribing physicians that poor compliance represents a potential problem, there have, until comparatively recently, been wide discrepancies between the highest and lowest estimates of compliance in patient populations. There is now convincing evidence to suggest that these wide discrepancies are associated with the methodology employed to estimate compliance, rather than to fundamental differences between patient groups and therapeutic regimens. In the past, estimates of compliance have largely been based upon counting the tablets returned at a clinic visit and it is now apparent that compliance can be greatly overestimated using this technique.

A greater insight into patients’ patterns of compliance has been gained from the use of a tablet container which incorporates a microprocessor to record the time and date of every opening (MEMS). The use of this device has broadened the concept of compliance from being simply a ‘yes/no’ phenomenon, dependent on whether a medication is taken, to a much better appreciation that compliance with a prescribed drug regimen has attributes of both quantity and time. Thus, a patient may appear to be fully compliant with respect to quantity of medication ingested but systematically introduces protracted intervals between doses, particularly where the regimen demands drug administration more than once a day. It is now clear that a common pattern of poor patient compliance is observed in the drug holiday pattern of dosage, involving omissions for 1 or more days, followed by a resumption of full-strength dosing.

Non-compliance and treatment outcome

Non-compliance has been directly associated with poorer treatment outcome in patients with a wide range of different conditions, including primary hypercholesterolaemia, diabetes, epilepsy, hypertension, coronary heart disease (CHD) and organ transplantation. However, these are more general treatment outcomes and in the case of cardiovascular disease it has proved possible to identify more specific implications of drug holidays. These consequences can be characterized as follows: (1) a period without effective drug action; (2) rebound effects when dosing is suddenly stopped; (3) excessive drug effects when dosing suddenly resumes; (4) financial.

The implications for these categories will be discussed, particularly with regard to their consequences on practical prescribing.
Period without effective drug action

The rebound effects when dosing is suddenly stopped and the excessive drug effects when dosing suddenly resumes are potential clinical consequences of drug holidays that characterize poor compliance. However, these potential risk implications are drug specific and will not occur with all cardiovascular therapies. In contrast, a period without effective drug action is potentially the most important clinical consequence of poor compliance, since it is not drug specific and since all drugs will eventually cease to have a pharmacological action at some time following cessation of therapy. The importance of this can be identified in a number of ways: the first is by inference, in that it has been demonstrated that blood pressure control is directly related to the rate of compliance with anti-hypertensive medication. Moreover, on a group basis it has been noted that levels of compliance must be maintained at about 90% to achieve benefit in terms of a fall in systolic and diastolic blood pressure with once-daily nitrendipine. In a study in individual patients treated with isradipine in a twice-daily dosing regimen, blood pressure responses were optimal only when the dosing interval was relatively short but were much poorer when the dosing interval was >10 h. It is reasonable to postulate from these studies and also from first principles that the difference between drugs in terms of their concentration-time profiles and their duration of action will lead to some agents being more effective than others in the face of interruptions in dosage.

This has led to the development of the concept of "therapeutic coverage." The principle underlying this concept is illustrated in Fig. 1 and it is clear that the parameter of therapeutic coverage utilizes information on a drug's pharmacodynamic duration of action, together with a profile of dosing history, and it reflects the percentage of time that the drug's action is maintained within the therapeutic range.

The difference in therapeutic coverage between different agents is well exemplified in a study, the design of which deliberately incorporated a pattern of non-compliance in a randomized, controlled manner. In this study, the efficacy and duration of response to betaxolol and atenolol were compared in response to sudden drug withdrawal. With respect to their peak anti-hypertensive effects and safety profiles, the two agents were comparable. However, on the basis of ambulatory monitoring, it was noted that the magnitude and duration of blood pressure response 24-48 h after a dose of betaxolol was statistically superior to those of atenolol and that this was compatible with the longer half-life of betaxolol. Thus, it is apparent that the differences between drugs with respect to their therapeutic coverage may well reflect their pharmacokinetic characteristics, particularly if there is a close relationship between plasma drug concentration and measured effect.

There is a widely held, and largely anecdotal, view that there is no relationship between the plasma concentration of an anti-hypertensive drug and its blood pressure lowering effect. It is now apparent, by application of integrated pharmacokinetic/pharmacodynamic modelling, that it is possible to characterize a mathematical description of blood pressure response in individual patients and, on this basis, direct relationships can be identified between drug concentrations and hypotensive effects.

The implications of all these observations are that haemodynamic effects of cardiovascular drugs are more likely to be sustained when serum drug levels are maintained at a consistent level over a steady-state dosage interval. This has been highlighted in studies with the calcium antagonist amlodipine and nifedipine in its long-acting formulation, GITS. Both these drugs sustain smooth blood concentrations and blood pressure responses over a steady-state dosage interval. The characteristics of these two agents observed in independent studies are illustrated in Fig. 2 and it is apparent that whilst amlodipine, with its intrinsic long half-life, can sustain an anti-hypertensive effect for at least 48 h (analogous to a missed dose), the response to nifedipine GITS begins to wane after 30 h as the drug formulation is exhausted and the natural elimination characteristics of nifedipine are apparent.
Rebound effects when dosing is suddenly stopped

The results of abrupt cessation of drug therapy and consequent rebound effects have been documented for a number of drugs. For example, a withdrawal syndrome frequently presents 18–48 h after the abrupt cessation of clonidine therapy. The syndrome is characterized by a rapid rise in blood pressure to above pre-treatment levels, headache, flushing, sweating, insomnia, nausea and vomiting. Withdrawal syndromes after the abrupt cessation of the use of β-adrenoceptor antagonists are also well recognized. While the frequency and severity of symptoms may be reduced by the use of cardio-selective agents and those with intrinsic sympathomimetic activity (ISA), it is clear that the use of non-selective β-blockers and those without ISA is associated with a withdrawal syndrome. This syndrome is characterized by palpitations, anxiety and hypertension above pre-treatment levels and the syndrome appears 24–48 h after the cessation of therapy.

The withdrawal syndrome is associated with increased risk. In a population-based case control study for the first events of CHD in patients with elevated blood pressure, it was noted that those patients who had recently stopped β-blocker therapy had a transient four-fold increase in relative risk of CHD and that this association was specific for β-blockers but not for diuretics.

Excessive drug effects when dosing suddenly resumes

This potential risk will not be observed with all therapies and thus may be regarded as drug specific. For example, with an anti-hypertensive drug the resumption of full-strength dosing following a drug holiday may well result in a marked fall in blood pressure or symptomatic first-dose postural hypotension. This phenomenon is more likely to occur with agents that are known to have a significant first-dose effect. For example, this is well recognized with the α-adrenoceptor antagonist, prazosin. Indeed, the U.K. Data Sheet for this agent warns that some patients may respond in an abrupt and exaggerated manner to the initial dose of the drug, evidenced by postural hypotension resulting in dizziness, weakness and, rarely, loss of consciousness upon commencement of therapy. A similar concern has been recognized with the angiotensin converting enzyme (ACE) inhibitors and, indeed, in Germany it is indicated in the fachinformation that ‘after the first dose of administration of the ACE inhibitor or following a dosage increment, the patients should be medically supervised for at least 6–8 h in order to prevent the development of an uncontrolled hypotensive response’.

If there is such concern following first-dose administration or dosage increments, it would seem reasonable that there should be equal concern about the patient who resumes dosing after serial dosage omission.

There is, furthermore, the possibility that excessive drug effect on dosage resumption may produce side effects characteristic of first-dose administration, such as the reflex tachycardia and flushing associated with early doses of the short-acting dihydropyridine calcium antagonists. In the susceptible, poorly-compliant patient, this may lead to a vicious circle where the patient perceives the drug-related side effect, ceases to take the therapy and then experiences the same side effect when dosing is resumed. The basis of such symptomatically-induced perturbation in compliance has been observed in a study with enalapril.

Financial consequences of poor compliance

Whilst not strictly a clinical consequence of poor compliance, it is very reasonable to assume that any financial implications of inadequate compliance may have secondary consequences with respect to healthcare provision. It has been clearly demonstrated that non-compliance with anti-hypertensive therapy has been associated with an increase in hospital admissions, length of stay and associated healthcare expenditure. Furthermore, based upon a literature review and application of a realistic cost model, it has been suggested that hospitalization due to non-compliance accounts for 11-7% of all healthcare expenditure in the U.S.A. and, when indirect costs are accounted for, the total costs of non-compliance are equivalent to 70% of healthcare expenditure on drugs.

There is compelling inferential evidence that improvements in compliance are associated with decreased healthcare expenditure. In a study of 274 Medicaid patients, who were receiving anti-hypertensive monotherapy with either verapamil (three times daily) or verapamil SR (once daily), and were evaluated over a 12-month period, there was evidence that, although the once-daily regimen was more expensive in terms of prescription costs, this was outweighed by a cost saving in other healthcare costs (physician, hospital and laboratory). This and other studies suggest that ‘improvements’ in compliance, which may in themselves have cost implications, ultimately result in cost benefit when total healthcare costs are evaluated.

Conclusion

It is now clear that poor compliance in a wide range of therapeutic areas is more prevalent than previously recognized. In particular, poor compliance is often characterized by serial dosage omissions or drug holidays. The implications of these drug holidays are particularly apparent in the treatment of hypertension and other cardiovascular disease and, whilst the emphasis on improving compliance by patient education must remain, it is more realistic (and ultimately of greater clinical relevance) to select drugs and dosage...
regimens which firstly do not exhibit the adverse events associated with drug holidays and, secondly, can provide good therapeutic coverage despite dosage omissions.

References