LEADING ARTICLE

Drug Safety 2002; 25 (7): 489-495
0114-5916/02/0007-0489/$25.00/0

Interrupting Drug Therapy in the Perioperative Period

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Abstract

Millions of patients undergo surgery each year and an increasing proportion of these patients are consuming therapeutic drugs. Drug therapy is often withheld in the immediate perioperative period and after major surgery, in particular, there is often a prolonged period of fasting. This may lead to withdrawal effects including recurrence or worsening of patients' disease symptomatology. These effects will occur during a period of physiological and pathophysiological stresses and render patients more vulnerable to drug withdrawal phenomena. Thus, patients may be exposed to greater and sometimes unnecessary risks in the perioperative period. There are relatively few studies that have investigated this problem. The ones that have, however, confirm that drug abstinence in the perioperative period is a relatively common phenomenon and one study has demonstrated an association between duration of drug abstinence and adverse outcomes.

The pathophysiological effects of major surgery on gastrointestinal function, neuro-humoral and cytokine adaptive responses to surgical stress are underappreciated. These responses can reduce the effectiveness of oral administration and exacerbate co-existing disease processes.

These problems are compounded by a fragmented approach to perioperative drug therapy with no one group of healthcare professionals assuming responsibility for this aspect of care. This may in part be a consequence of the complexities of rationalising drug therapy in the perioperative period together with the lack of readily available and evidence based information strategies for individual drugs or drug classes. An additional problem relates to the formulations, inherent pharmacokinetics and limited routes of administration of many prescribed drugs. These can prevent a 'seamless' transition from preoperative to postoperative management.

Consumers, health professionals, pharmaceutical companies and drug regulatory agencies must all play a part in rectifying this problem. There remains a need for further research to clarify the effects of abstinence on patient outcomes and also to identify optimum strategies to avoid unwanted drug abstinence.

Worldwide, millions of patients undergo surgery each year under general or regional anaesthesia. Many of these patients will be taking drugs for therapeutic benefit. Even with increased use of non-invasive surgical techniques, a proportion of these patients will undergo major surgery and have a period of enforced drug abstinence during preoperative and postoperative fasting. Such enforced abstinence will at best lead to loss of effect, but for some drugs will lead to recurrence or worsening of the patient's disease symptomatology.[1] Contrary to the views of some, it is evident that these, so called type E reactions (*E*nding of use), are not so uncommon:[2] their importance being particularly relevant in patients undergoing major abdominal surgery. Moreover, after major surgery this drug withdrawal occurs against a backdrop of physiological and pathophysiological stresses,[3] which may render patients more vulnerable to these effects. Although there are potential solutions that can be implemented locally by healthcare professionals these problems would benefit from greater attention by the pharmaceutical industry as well as drug regulatory agencies.[1]

1. Published Studies of Therapy Interruption

Although many millions of patients will as part of their medical care have their usual medication interrupted for surgery, the pathophysiological consequences and resultant outcomes have been relatively little studied.

In 1984, Duthie et al.[4] reported a prospective study of 216 patients in the UK undergoing surgery. One-third of patients were taking long-term medication and half of those were taking medication for cardiovascular diseases. Over one-quarter of this latter group did not have their medication prescribed preoperatively and over 60% did not receive their medication on the day of surgery.[4] In another UK study, Wyld and Nimmo[5] found that approximately 30% of prescribed drugs were not given on the day of and the day after surgery.[5] Similarly, Kluger et al.,[6] in an Australian study of 241 patients, reported that 44% of patients were receiving medication prior to hospital admission and that cardiovascular medication accounted for the largest proportion of prescriptions (41%). Almost half of the patients did not receive their drugs on the day of surgery and approximately one third did not receive their drugs on the first day after operation.[6] The most common reasons were that drugs were 'withheld because of fasting' (49%) and 'failure to prescribe'. These studies were of relatively unselected patients and likely to underestimate the effects in critically ill patients or those undergoing major procedures. Objective evidence that this aspect of care has improved since these studies were published is lacking.

More recently, Kennedy et al.[7] conducted a prospective observational study in over 1000 patients admitted for elective or emergency surgery to identify: (i) the drug usage profile of the general surgical population; (ii) those patients at greatest risk of polypharmacy and quantify the relative importance of those drugs to surgical outcome; and (iii) the frequency and duration of drug withdrawal and relate this to the post operative outcome. The study found that nearly half of the patients in the study were taking drugs unrelated to their surgical conditions. The mean number of these drugs increased with age, and was greatest for patients admitted for vascular surgery and other major procedures. Of those patients taking drugs unrelated to surgery, almost 50% were taking drugs for cardiovascular problems. Two hundred and thirty-five patients experienced 373 complications following surgery. Taking a drug unrelated to the underlying surgical condition was associated with an increased relative risk of a postoperative complication of 2.7 compared with those who were not taking any drug. There was also a positive correlation between the duration of drug withdrawal and the complication rate. Of patients taking a cardiovascular medicine and who had their regular medication withdrawn for more than 1 day, 14% experienced a cardiac complication. Five percent of patients who had undergone surgery experienced postoperative complications directly attributable to withdrawal of their regular medicines. In all

cases reintroduction of drug therapy was curative, supporting but not proving a more general causal relationship between drug withdrawal and postoperative complications.

In addition to the studies described above, many anecdotal cases of drug withdrawal phenomena in patients undergoing surgery have also been reported over the years. In contrast, one case-control study using multivariate analysis from the UK concluded that with the possible exception of nitrates, long-term pre-operative drug treatment did not increase the odds of cardiac death.[8] However, this study was retrospective, the authors acknowledged its low statistical power and methodologically it is less compelling than the prospective study of Kennedy et al.[7]

Of note, withdrawal of drugs in a variety of other non-acute and experimental settings has shown to be detrimental and supports the concept that withdrawal of drug therapy in the perioperative period may be harmful (table I).[9-12] Withdrawal symptoms can have many guises, for example abdominal pain following withdrawal of tricyclic antidepressants,[11] which might confound surgical assessment of the patient.

However, considering the potential size of the problem there remains a paucity of good data to adequately evaluate the scale of effect of drug withdrawal on postoperative outcomes.

2. Effects of Surgery on Drug Absorption and the Effects of Surgical Stress

There is an under-appreciation of the physiological and pathophysiological consequences of surgery.[3,13,14] Drugs are normally taken orally, but the effects of surgery and critical illness on gastrointestinal function may reduce the reliability of this route.[15-22] First, gastric emptying may be impeded, by surgery, by postoperative opioid analgesics as well as by catecholamine drug infusions.[20,21] Less commonly the absorptive capacity of the gut may also be impaired.[22] These factors contrive to reduce the efficacy of oral medication even if it is given to the patient. Moreover, the emergency surgical patient may not have had their medication for some time before presenting to hospital because of surgical illness. Abstinence may continue in hospital while the patient is being prepared and waits for surgery, which may not be immediate. These patients may then be particularly predisposed and vulnerable to inadvertent drug withdrawal and it is noteworthy that they constitute the highest risk patients for morbidity and mortality in audits of surgical mortality. Process of care errors, such as drugs not prescribed, or the universal application of not giving oral drugs to fasted patients, can also add to these problems in all categories of surgical patient.

Surgery has profound effects on neuroendocrine and metabolic responses with activation of

Table I. Potential adverse effects of drug withdrawal

Drug class	Potential effects
Hypnotics/anxiolytics	Anxiety, confusion, convulsions
Anticonvulsants	Convulsions, hypoxia, aspiration pneumonia
HIV drugs	Drug resistance
Antiparkinsonian drugs e.g. levodopa, amantadine	Immobility, pulmonary complications
Antianginals	Angina, acute coronary syndromes
Antihypertensives	Hypertension
Drugs for heart failure	Cardiac failure, poor tissue healing
Oral hypoglycaemics	Hyperglycaemia, infectious complications
Anticoagulants	Thrombosis, embolism, acute coronary syndrome
Corticosteroids	Addisonian crisis
Antidepressants	Exacerbation of disease symptomatology and specific withdrawal syndromes
Antipsychotics	Psychiatric disturbances and extrapyramidal syndromes

the hypothalamic-pituitary-adrenal axis, activation of the renin-angiotensin system, increased secretion of vasopressin, other hormones, catecholamines and cytokines.[3,13,23] Over and above this, there may be complications such as hypotension and other haemodynamic disturbances at induction of anaesthesia, postoperative hypoxaemia, postoperative pain and co-existing overt or undiagnosed diseases as well as potential for drug interactions.[24-27] The scene is set whereby drug withdrawal is occurring at a time when a variety of surgical stresses are manifest and patients are likely to be more vulnerable to the consequences of inadvertent drug abstinence. When this is considered against a background of multiple pathology and polypharmacy in an ageing population, the potential for adverse outcomes is considerable.

3. The Role of Local Professionals, Drug Regulatory Authorities, the Pharmaceutical Industry, and Information Technology

The under appreciation of the potentially harmful effects discussed so far are compounded by a fragmented approach to perioperative pharmacotherapy. Many practitioners have some input including junior ward doctors, senior surgeons, anaesthetists, medical specialists, pharmacists and nurses. However, it is often the case that no one individual or group assumes responsibility for these problems.

Sources of detailed advice on management of individual drugs or drug classes in the postoperative period are scarce. Textbooks in general offer little advice.[28,29] National Formularies such as the British National Formulary contain little information as do most drug data sheets. In their study, Kluger et al.[6] contacted 45 companies for advice on drugs with potential adverse effects in the perioperative period. Only two showed great interest, and 20 companies did not reply at all. For the busy prescriber and the ward pharmacist information on best or current practice is not readily accessible.

While the European Union and other countries' drug regulatory agencies demand patient information inserts, even for intravenous drugs such as suxamethonium chloride that will never be self-administered by patients, there appears to be no requirement for drug companies to provide strategies to deal with patients unable to take their medicines orally. Moreover the costs of licensing and producing alternative non-oral formulations with their limited profitability do not act as incentives for the pharmaceutical industry to highlight or tackle this potential problem. For example, while intravenous *N*-acetylcysteine has been commercially available in the UK since 1979 it remains unavailable in the USA approximately 20 years later. This has necessitated filtering the oral preparation before administering it intravenously to patients unsuitable for oral therapy.[30] Surely drug regulation agencies and industry have failed clinicians and their patients in such instances?

The issues for prescribers are complex. Some drugs will have non-oral alternatives while others will not. Some will have a within-class or adequate out-of-class non-oral alternative. However, for some drugs there are no satisfactory alternatives. While most drugs are best continued, a minority should be discontinued before surgery.[12] For some conditions, where multiple drugs are required, the issues are particularly complex.[31,32] Pharmacokinetic and pharmacodynamic factors will determine the offset of effect. However, the interplay of these two factors in the context of major surgery make predictions of the rate of offset difficult. For example, propranolol and pindolol have almost identical half-lifes but they differ considerably in their rate of decline of β-blocking effects.[33] This has been attributed to their different pharmacological effect versus concentration relationship. This illustrates the difficulties for even the pharmacologically astute clinician. It is also noteworthy that, in other situations, use of basic pharmacokinetic parameters such as half-life to predict offset of drug effect can also be misleading.[34,35]

Patients with ischaemic heart disease, a major contributor to perioperative morbidity and mortality, illustrate some of these difficulties. Many

of these patients will be taking, for very clear evidence-based reasons, a combination of aspirin (acetylsalicylic acid), an HMG-CoA reductase inhibitor, β-blocker, ACE inhibitor, nitrate, diuretic, with or without other antihypertensives and oral hypoglycaemic agents. For major surgery, some of these can safely be withheld for several days (aspirin and the HMG-CoA reductase inhibitor), some should be changed temporarily (oral hypoglycaemics to insulin), while the sudden withdrawal of β-blockade might be dangerous. ACE inhibitors are a two-edged sword – from the point of view of left ventricular dysfunction they are better continued, but if continued there may be an increased risk of troublesome hypotension and renal impairment, particularly if fluid balance is deranged perioperatively. Decisions about optimal therapy in such circumstances require close liaison between surgeon, anaesthetist and appropriate medical specialist. These should not be delegated to inexperienced junior medical staff.

Given these complexities, perioperative pharmacotherapy requires an active, tailored approach. Moreover, the pressures for fast-track surgery and wider application of day-case or ambulatory surgery to patients previously admitted to hospital prior to operation mean healthcare professionals, including those in primary care, require rapid access to reliable information about best practice.[36] The current absence of such information undoubtedly contributes to what appears to be the present day passive, laissez-faire approach to peri-operative pharmacotherapy.

4. Recommendations

If it is accepted that most available evidence points to potential or actual detriment to patients from inadvertent drug withdrawal then action at several levels will be required to redress the problem.

Patients and patient groups should become more proactive and challenge health professionals and organisations as to how they will continue to receive the therapeutic benefits of their drug therapy while they are hospitalised.

Healthcare professionals need to adopt an integrated and proactive package of measures to ensure important drug therapy is not needlessly discontinued. Pharmacists might have an enhanced role at ward level and perhaps in pre-admission clinics. Primary care workers and others seeing the patient prior to admission could identify potential problems and formulate plans to deal with them in advance of their admission.[37] Ideally, preoperative assessment for elective surgery should not be an occasion to agonise over the potential difficulties ahead but rather an opportunity to re-examine the indications and contraindications for drug treatment and if necessary to rationalise prescribing by changing or withdrawing medications. Wherever possible drug therapy should be evidence-based. Medications can be substituted to improve compliance and modified to achieve therapeutic targets – for example control of blood pressure, blood glucose, pulmonary function, etc.

Where possible and desirable, drugs should be continued throughout surgery. It should be noted however, that a minority of drugs, (e.g. oral hypoglycaemics, biguanides, monoamine oxidase inhibitors), are recommended to be discontinued prior to surgery. For some drugs the benefits and risks of continuation remain uncertain (e.g. ACE inhibitors). Reinstitution of drug therapy may be achieved more rapidly if measures to 'rehabilitate the gut' following surgery are implemented.[1,38,39] These might include placement of jejunal enteral tubes bypassing the common problem of gastric stasis, using prokinetic drugs promoting delivery of drugs into the small bowel as well as reducing surgical trauma with minimally invasive surgery and thus opioid requirements. Opioids, which commonly contribute to gastrointestinal stasis, may also be avoided or reduced with the use of alternative analgesic regimens such as epidural and major regional local anaesthetic techniques and greater use of simple analgesics such as non-steroidal anti-inflammatory drugs. These in turn need to be used with caution because of the risks of intestinal problems, renal dysfunction, and adverse drug interactions, particularly in the elderly.

However, in future, use of peripherally acting opioid antagonists such as methyl-naltrexone or ADL 8-2698 may allow patients the benefits of good analgesia and early restoration of normal medication by the oral route.[40,41] Where gut function cannot be rapidly restored alternative strategies must be sought; for some drugs there may be no imperative to continue therapy. For others, alternative routes of administration of the same drug or drug class will provide the solution. These include buccal, sublingual, rectal, transcutaneous and inhalational modes of administration. Other drug classes available by these alternative routes may adequately substitute and provide satisfactory control of disease symptomatology. However, these strategies will not be suitable for all situations.

A specific drug prescription chart was shown to improve process of care for oxygen therapy and introduction of such a tool for perioperative drug therapy in general might also be expected to lead to improvements.[42] Regular audit of perioperative drug therapy will also act as a stimulus to improvement.

However, given the complexities of deciding the best strategy for each drug, busy prescribers need readily accessible and reliable information. Currently this is not available in many local or national formularies nor in most data sheets. This should be rectified as a matter of urgency. Moreover given the sophistication of current information technology it is surprising and disappointing that in this arena (and in others) that it is not used to guide prescribers. Woosley, in another context, has made the pertinent comment that, '(The US) society has invested in developing wondrous new pharmacological therapies but has failed to invest adequately in their safe use'.[43]

Drug regulatory agencies should demand better information in data sheets for prescribers and expect information from pharmaceutical companies, on the management of patients who cannot tolerate oral medication, in their application for a drug license. It is of interest that, in the UK at least, patients on older types of cardiovascular medication for hypertension or heart failure such as methyldopa, hydralazine, clonidine, β-adrenergic antagonists, nitrates and digoxin will have the benefit of parenteral preparations should the oral route be precluded. However, for the newer agents, such as calcium channel blockers, ACE inhibitors and angiotensin receptor antagonists, parenteral preparations are unavailable. Is this coincidence or are pharmaceutical companies too concerned with economic or perceived safety issues related to parenteral formulations of drugs? Pharmaceutical companies should give greater consideration to these problems and drug regulatory agencies should be more responsive to the needs of prescribers and patients.

While these improvements are implemented there remains an urgent need for further research to better define the scale of the problem of drug abstinence peri-operatively and in the critically ill as well as to identifying the best strategies for dealing with these problems.

5. Conclusions

The currently available evidence suggests that patients can be adversely affected by inadvertent drug withdrawal before and after surgery. Although the causes and solutions are multifaceted and complex, it is nevertheless time for a wake-up call for all those involved in the process. Healthcare professionals, pharmaceutical companies and drug regulation agencies must all play their part in rectifying this area of neglect, otherwise we will continue to stand accused of failing large numbers of patients during their surgical or critical illness. In particular there must be a political will for change.[44]

Acknowledgements

The authors have received no funding for the preparation of this manuscript nor have any conflicts of interest directly relevant to the contents of this manuscript.

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