0022-3565/11/3392-324–328$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
JPET 339:324–328, 2011

Vol. 339, No. 2
183285/3725538
Printed in U.S.A.

2011 Torald Sollmann Award Lecture

Drug Discontinuation Effects Are Part of the Pharmacology of a Drug

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Received April 25, 2011; accepted August 16, 2011

ABSTRACT

Most reviews of drug withdrawal effects focus on drugs of potential abuse such as opioids, benzodiazepines, etc. Abrupt discontinuation of many other drugs used in medicine cause withdrawal syndromes, some of which can be fatal. Discontinuation of a number of cardiovascular drugs can increase risk of cardiovascular events above that of people not taking these drugs. These include β-adrenergic receptor antagonists, aspirin, HMG-CoA reductase inhibitors (statins), and heparin. Rebound hypertension occurs after abrupt cessation of many antihypertensive drugs. The possibility of discontinuation syndromes has usually been neglected until adverse clinical events force them to be noticed. Attention to the possibility of drug discontinuation effects is an important part of drug safety evaluation.

Introduction

Dr. Torald Sollmann was a distinguished pharmacologist at Western Reserve School of Medicine (Cleveland, OH) from 1898 to 1944. He was the author of a major textbook, *Manual of Pharmacology*, that continued for eight editions .

The Torald Sollmann Award has always represented to me the recognition of an outstanding pharmacologist for lifetime achievements. What an honor you, ASPET, have given me by adding me to the list of previous recipients. Thank you so very much.

There are four people I want to especially thank for their help over the years enabling me to accomplish what I have done. First, and most important, is June, my wife of 54 years. She has been my major enabler for a lifetime. Second is Roger Sevy at Temple University (Philadelphia, PA). He brought me into pharmacology when I was a second-year medical student and later into ASPET, taught me how to do research, and guided me for the first 20 years of my professional life. Then, when I went to Cornell, Wally Riker at Cornell and John Burns at Hoffmann-La Roche (Nutley, NJ) were key enablers for the next phase of my career. What I have accomplished is a result of the help of these four people and the help of all of the students, fellows, collaborators, and colleagues I have had for the past 55 years. My thanks go to all of them.

Today, I want to talk, not about past activities, but about a future need, the need to identify the likelihood of a drug discontinuation syndrome before it causes preventable human tragedies. But first, a brief survey of some of my prior work for those interested.

After thalidomide, adverse drug reactions became a topic for study. Most epidemiologist investigators, usually with infectious disease backgrounds, assumed that an event that could be caused by a drug and followed taking that drug was caused by that drug. We did a study, adverse nondrug reactions (Reidenberg and Lowenthal, 1968), demonstrating that people not taking any drugs could still have symptoms that were the same as those symptoms caused by an adverse effect of a drug. It proved the need for controls in adverse drug reaction studies just as for drug efficacy studies. I then became a member and was elected vice-chair of the Joint Commission on Prescription Drug Use, helping to establish scientific drug epidemiology as an integral part of pharmacological science.

Recognizing that impaired kidney function led to a high frequency of adverse drug reactions, I did research on how

This work was supported in part by the National Institutes of Health National Center for Research Resources [Grant UL1-RR024996]; and a Cooperative Agreement from the Agency for Healthcare Research and Quality [5U18HS016075].

Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.

doi:10.1124/jpet.111.183285.

ABBREVIATION: ASPET, American Society for Pharmacology and Experimental Therapeutics.

kidney failure modified dose response and then wrote a monograph titled: "Renal Function and Drug Action" in 1971 (Reidenberg, 1971). In addition to looking at renal function, I showed that age was an independent variable affecting dose-response (Reidenberg et al., 1978). Because by the early 1970s much was known about why individuals differed in their responses to drugs, I organized an American College of Physicians postgraduate course, "Individualization of Drug Therapy," subsequently published as a book (Reidenberg, 1974). Now, under the name of "personalized medicine," this concept is a major theme of medical research. I helped to legitimize palliative care at a time when care was focused on cure by organizing an American College of Physicians course, "Clinical Pharmacology of Symptom Control," with later publication in book form (Reidenberg, 1982). With much help from my wife, I edited *Clinical Pharmacology and Therapeutics* for 17 years from 1985 to 2001 when it was cosponsored by ASPET. I have been a member of the World Health Organization Expert Panel on the Selection and Use of Essential Drugs since 1989 and a member of eight of its expert committees, being elected chair of two. So much for the past, now let us consider a need for the future.

Drug Discontinuation Syndromes

Drug withdrawal effects are usually disregarded in pharmacology and medicine until adverse clinical events force them to be noticed. A classic example of this is abrupt withdrawal of propranolol in patients with coronary disease, causing angina pectoris. Aggravation of angina and deaths occurred (Slome, 1973; Alderman et al., 1974). Despite this experience more than 35 years ago, the risk of sudden cardiovascular medication withdrawal causing severe illness and death continues to be neglected. The recent demonstration of increased mortality after discontinuation of low-dose aspirin prophylaxis, especially in the first 5 to 7 days after stopping aspirin (Sung et al., 2010), indicates the need to think comprehensively about drug discontinuation syndromes. They are not limited to drugs with abuse or addiction potential but also occur after discontinuation of therapeutic drugs. Recent examples include aspirin (Sung et al., 2010), statins (Cubeddu and Seamon, 2006), and heparin (Bijsterveld et al., 2003). Usually we pay no attention to the possibility that a drug without addiction liability can cause a discontinuation syndrome until a clinical catastrophe occurs and is identified as caused by discontinuation of the drug. The possibility of medication discontinuation syndromes arising on cessation of chronically administered drugs requires more attention to reduce the harm discontinuation may cause.

When a drug is stopped, the underlying state can recur. This unmasking of the underlying state, such as recurrent hypothyroidism when full replacement dose of thyroid medication is discontinued, needs no further explanation. The other withdrawal syndromes seem to have different biological bases. In general, the body can adapt in some way to the effect of drug administered at a high enough dose for a long enough period of time to induce the adaptation. When the drug is discontinued, the body eliminates the drug more rapidly than the adapted state subsides. The persistence of the adapted state in the absence of the drug leads to the withdrawal or discontinuation effects. When the discontinuation leads to enhanced disease activity, it can be difficult to differentiate from simply recurrent disease and hard to recognize. Here are some examples of cardiovascular disease exacerbations with some fatalities after cessation of specific cardiovascular drugs.

Aspirin

In 1983, data suggested that certain populations of platelets had enhanced cyclooxygenase activity 5 days after aspirin ingestion (McDonald and Ali, 1983). In 1990, urinary excretion of both 6-keto-prostaglandin F1α and thromboxane B2 were found elevated 2 weeks after aspirin was stopped (Vial et al., 1991). Three years later, Mousa et al. (1993) showed that although platelets are inhibited by a single dose of aspirin, 6 days after the dose, fibrinogen binding to activated platelets was increased over baseline as was arachidonic acid-induced platelet aggregation. In 1996, the effect of aspirin discontinuation on fibrin-fibrinogen was shown (Fatah et al., 1996). Collet et al. (2000) reported that acute discontinuation of chronic aspirin therapy seemed to raise the risk of acute coronary thrombosis. Thus, by 1990 there was biological evidence, and by 2000 there was clinical evidence, of a potential aspirin discontinuation effect increasing the risk of thrombotic events. But it took until 2010 for a definitive study of aspirin discontinuation effects including fatalities to be published (Sung et al., 2010). The topic of rebound effect caused by discontinuation of aspirin, clopidogrel, and even prasugrel has been reviewed with the severe adverse clinical consequences described (Lordkipanidzé et al., 2009) and the risk for enhanced ischemic stroke articulated (Sibon and Orgogozo, 2004).

Heparin

In 1992, a randomized placebo-controlled clinical trial comparing aspirin, heparin, both, or neither, in unstable angina found that within 96 h of discontinuation of study drug reactivation of disease occurred in 14 people who received heparin but in only five in each of the other three groups (Théroux et al., 1992). (The aspirin effect inhibiting platelet cyclooxygenase lasts more than 96 h.) In 2002, activation of coagulation above baseline values was shown to occur within 6 to 12 h of stopping heparin (Bijsterveld et al., 2002). A clinical trial in 2003 confirmed this clinical phenomenon of exacerbation of disease and not merely unmasking of disease on discontinuation of heparin (Bijsterveld et al., 2003).

HMG-CoA Reductase Inhibitors (Statins)

Thomas and Mann (1998) noted patients that were switched to a new statin at less than equivalent dose of prior statin had a tripling of their cardiovascular event rate over the next 6 months. Four years later, Heeschen et al. (2002, 2003) found a trend that patients taking statins whose statins were stopped when they were hospitalized had worse outcomes over the next month than patients who never took statins. Another epidemiologic study involving 174,635 patients showed that patients who stopped statins on admission for acute myocardial infarction developed more heart failure, ventricular tachycardia, or death during hospitalization than patients never on statins (Fonarow et al., 2005).

Other studies have found discontinuing statins leads to worse cardiovascular outcomes in the near term compared with continuing statins (Blanco et al., 2007; Schouten et al., 2007; Risselada et al., 2009).

Studies in humans have shown that statin discontinuation causes impairment of nitric-oxide release so that measures of endothelial function are worse than at baseline (Laufs et al., 2001; Rosengarten et al., 2007; Chen et al., 2009). Another study of patients with acute myocardial infarction found that those patients on statins before a heart attack who discontinued them on admission had higher C reactive protein levels 5 days after the infarction than patients never receiving statins (Sposito et al., 2009).

Calcium Channel Blockers

Verapamil was first used as an antiarrhythmic drug in 1971. A report of a withdrawal syndrome producing arrhythmia and angina reported in 1983 presented five cases of discontinuation of calcium antagonists causing severe cardiac morbidity out of 143 patients stopping calcium antagonists, an incidence of 3.5% (Subramanian et al., 1983). A study in 1992 showed that verapamil given to rats up-regulated the sodium channel mRNA level up to 3-fold (Duff et al., 1992). Those authors noted the likelihood of a discontinuation syndrome of arrhythmias caused by the consequences of this effect. Despite the data in Subramanian et al. (1983), a review of calcium channel-blocking drugs in 2001 makes no mention of the presence or absence of a drug discontinuation syndrome (Kizer and Kimmel, 2001). Neither does the 2009 Food and Drug Administration-approved label of verapamil.

α-Adrenergic Receptor Antagonists

It is known that abrupt discontinuation of many antihypertensive drugs can cause rebound hypertension (Houston, 1981). Drugs that act on the sympathetic nervous system, clonidine, α-methyldopa, and β-adrenergic receptor antagonists clearly have this effect. Whether abrupt discontinuation of α-adrenergic receptor antagonists that lower blood pressure cause rebound hypertension is not known. A study found subjects with diastolic blood pressure above 90 mm Hg at baseline had a fall of 8 mm Hg on terazosin (Debruyne et al., 1996). No mention was made about what happened to the blood pressure of those patients when the terazosin was stopped. A study of tamsulosin found that after treatment for 1 year the blood pressure in the initially uncontrolled hypertension group averaged 15/9 mm Hg less than at baseline (Lepor, 1998). No measurements were reported after cessation of tamsulosin to learn what happened to the blood pressure in those patients. Whether rebound hypertension occurred in any of these people after stopping their α-adrenergic antagonist is not known (Lowe, 1994). It does occur when a variety of other drugs that lower blood pressure are abruptly stopped.

Digoxin

Patients with chronic stable heart failure being treated with diuretics, an angiotensin-converting enzyme inhibitor and digoxin, were randomized to continue digoxin or take placebo. Worse heart failure occurred in 23 of 59 patients randomized to placebo but in only 4 of 61 on digoxin (Packer et al., 1993). Whether the inhibition of sodium-potassium ATPase by digoxin causes up-regulation of the enzyme with discontinuation of the drug causing low intracellular calcium is not clear. Knowing whether an abrupt discontinuation effect occurs after stopping digoxin would be helpful because it continues in limited use, is still considered essential, and is included in the 2011 World Health Organization Model List of Essential Medicines (http://www.who.int/medicines/publications/essentialmedicines/en/).

Withdrawal Syndromes

These examples of recently described discontinuation and potential discontinuation syndromes illustrate some of the issues concerning drug discontinuation effects. A review of Food and Drug Administration approvals of new molecular entities in 2008 and 2009 listed 27 compounds. Many were for short-term use. Others had statements about withdrawal but those drugs were in classes with prior information known about withdrawal risks of those classes of drugs. However, four drugs, a calcium channel blocker, an α-adrenergic receptor antagonist, and two opioid receptor antagonists, had no statements of any sort about withdrawal in the labeling. Whether any of them, if taken chronically and then abruptly stopped, would cause a withdrawal syndrome is a reasonable question. The data on calcium channel blockers and blood pressure-lowering drugs having discontinuation effects and the data suggesting the speculation about rebound hypertension after discontinuing α-adrenergic receptor antagonists have been presented above. Yoburn et al. (1988) found that treatment of mice for 1 week with naltrexone, an opioid receptor antagonist, up-regulated all classes of opioid receptors. After naltrexone was stopped, they found supersensitivity to opioid administration, a drug discontinuation effect.

There are several problems with addressing the topic of medication withdrawal syndromes. One is recognition of the existence of a withdrawal effect after discontinuing a medication. Another is describing the syndrome including its time course and incidence. A third is developing rational and, if possible, evidence-based recommendations for prevention or management of the syndrome. Initial recognition has often been described in case reports by astute observers. Subsequent studies may use observational rather than experimental clinical studies. Whether the association between drug discontinuation and events is causal may be uncertain. In the examples cited, laboratory data demonstrating biologic plausibility of the withdrawal effects contributed to the understanding of causality. Recognizing that exacerbation of disease is caused by medication discontinuation can be very difficult. A comparative evaluation of groups is necessary.

My hypothesis is that the discontinuation effects are caused by the biologic adaptation to the drug persisting after the drug is cleared from the body. This hypothesis predicts that discontinuation effects begin several half-times after the last dose and will dissipate a number of half-times later. This time course of discontinuation effects has great relevance in the context of outpatient nonadherence to chronic medication schedules. To illustrate this relevance, here are a few examples of the frequency of patients discontinuing their cardiovascular medications:

1. Approximately 50% of 4783 patients in 21 phase 4 studies of antihypertensive drugs had stopped their medication

within 1 year. Drug holidays of 3 or more consecutive days of omitted medication were common (Vrijens et al., 2008).

2. Studies of a variety of chronic cardiovascular medications gave discontinuing rates of 8 to 22% (Eagle et al., 2004).
3. A study of charts of 124 elderly outpatients for drug discontinuations during a 1-year period was to identify adverse events. Discontinuation of 66 cardiovascular drugs produced 72 adverse events using the Naranjo criteria for causality. Five cardiovascular drugs discontinued caused six physiological withdrawal events during the first month after discontinuation. These were exacerbations of heart failure and/or hypertension. The other events were described as simply exacerbations of disease not caused by acute discontinuation effects (Graves et al., 1997).

Identifying Potential for Discontinuation Syndromes

Drug discontinuation effects can occur and are usually neglected in pharmacology and medicine until adverse clinical events force them to be noticed. Even after being noticed, few resources are made available to evaluate their frequency and determine the best way to manage them. There are several ways to overcome this neglect and at least identify the potential for discontinuation effects and their frequency.

Modern pharmacology has usually identified the biochemical and molecular action of most drugs. For drugs given chronically, one can look for laboratory evidence of adaptation to the drug. If such adaptation occurs, it is likely that, after discontinuation, the body will eliminate the drug more rapidly than the adaptation will subside. Any laboratory evidence of adaptation or of an effect shortly after drug discontinuation should be interpreted as presenting a potential discontinuation syndrome. For drugs in clinical trials, observations can continue for an appropriate period of time after the drug is stopped to learn whether events occur that could be caused by drug discontinuation. For drugs in clinical use, large databases are now being developed for doing comparative effectiveness research (Mushlin and Ghomrawi, 2010). Perhaps epidemiologic techniques can be developed to learn whether discontinuation syndromes exist, too.

Conclusion

Drug discontinuation effects are well known for some classes of drugs. Opioid withdrawal was known in Roman times (170 AD), since Scarborough (1995) described the physician Galen's comments about his treatment of Marcus Aurelius with opium as not leading to addiction. This implies that Galen knew about addiction and therefore drug withdrawal. Medical focus has continued to be on psychoactive drugs with attention on selective serotonin reuptake inhibitors (Black et al., 2000) and benzodiazepines (Petursson and Lader, 1981). Even endocrine drugs have withdrawal syndromes (Hochberg et al, 2003). Recommendations have been to taper rather than abruptly discontinue all of these drugs because early studies with barbiturates indicated that the severity of the withdrawal effects was a function of the rate of fall of drug concentration in the blood of the subject (Jaffe, 1980).

Despite all of this knowledge, the possibility of drug discontinuation syndromes has usually been neglected until adverse clinical events force them to be noticed. We should consider discontinuation effects as part of the pharmacology of the drug. Attention to the possibility of drug discontinuation effects is an important part of drug safety evaluation.

Authorship Contributions

Participated in research design: Reidenberg.
Conducted experiments: Reidenberg.
Performed data analysis: Reidenberg.
Wrote or contributed to the writing of the manuscript: Reidenberg.

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