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The use of drug calendars for the diagnosis of cutaneous drug eruptions in the age of electronic medical records

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Abstract

A morbilliform drug eruption is the most common condition leading to a dermatology consultation for a patient in the hospital. Timing is an important diagnostic tool since the onset of a skin rash usually takes place within days-to-weeks of the start of the implicated drug. A comprehensive, thorough, and reliable drug history by the clinician is essential. Therefore, to assist in the task of determining the causative medication of a new skin rash in a hospitalized patient, the creation of a drug calendar is recommended. The development of an electronic version of the drug calendar offers several benefits over the manual version. As the use of electronic medical records continues to become the standard in medicine, the electronic drug calendar will serve as an invaluable tool for the diagnosis of drug hypersensitivity.

Keywords: calendar, cutaneous, diagnosis, drug, electronic, eruption, medical, record

Introduction

The most common condition leading to a dermatology consultation in the hospital is a morbilliform drug eruption. Hospitalized patients routinely receive an average of 12.5 medications during the course of their hospitalization making it difficult to identify the causative agent of the drug hypersensitivity reaction [1]. The onset of a drug-related skin rash usually takes place within days-to-weeks of the start of the implicated drug making timing an important diagnostic tool. The clever clinician attempts to determine which drug was the culprit and then substitute and/or stop just one medication — not all of them.

Discussion

Drug history by clinician

There is no substitute for a comprehensive, thorough, and reliable drug history by the clinician. Indeed, a complete drug history should be obtained, which includes the six "Ins" of drug use that were described by Dr Joseph Bikowski in 2009: 1) instilled (drops placed in the ears, eyes, or nose), 2) inhaled (nasal sprays and mists, inhalers, or nebulizers. Nebulizers in particular are used in cystic fibrosis and human immunodeficiency (HIV)-positive patients with resistant recurrent pneumonias and often contain inhaled antibiotics or aerosolized pentamidine, 3) injected (drugs given intramuscularly, subcutaneously, or intravenously), 4) inserted (a drug inserted into any orifice, such as vaginal or anal suppositories), and 5) in secret (surreptitious self-administration of a legal medication, an illegal substance, or a recreational drug), [2]. Therefore, the complete drug history should include over the counter medications, non-prescription drugs, vitamins, dietary supplements containing herbal or organic products, and alternative or complementary medications.

Manual drug calendar

The creation of a drug calendar or a graphical drug chart can assist in the task of determining the

causative medication of a new skin rash in a hospitalized patient [1]. Typically, the drug calendar is a labor-intensive, time-consuming paper chart with handwritten dates and medications. However, the drug calendar will not detect the surreptitious use of medication, the use or abuse of illegal substances, or even over-the-counter medications, vitamins, and supplements. Therefore, specific questioning of the patient may unmask these unusual causes of drug rashes.

Electronic drug calendar

An electronic version of a drug calendar can be created with the assistance of the information technology department of the hospital. The drug calendar would list the daily medications administered over days to weeks before the onset of a drug rash. The development of an electronic version of the drug calendar offers several benefits over the manual version.

Universal availability of drug history

The electronic drug calendar produced by the dermatology consultant is available to all members of the health care team. This includes not only the prescribing doctor, but also the pharmacist ordering the drug to the floor and the nurse dispensing the medication. In addition, it can be accessed from anywhere in the medical center.

Medications received away from the bedside

Electronic generation of the drug calendar should eliminate possible errors in transcription. In addition, the electronic drug calendar should include medications administered at sites other than the bedside. These would include drugs not only given for radiology studies, but also those administered during procedures performed by other clinicians such as cardiologists, surgeons, or other subspecialists.

Several agents used by radiologists and radiation oncologists would be part of the electronic drug calendar. For example, iododerma — a dramatic vesiculo-pustular eruption of the face and hands — is a well-known skin rash from iodinated contrast media routinely reported on radiology procedure forms [3]. Also, it took years to relate nephrogenic systemic fibrosis to the gadolinium-based contrast agent administered intravenously during magnetic resonance imaging because gadolinium was considered to be safe and was not even listed on the procedure forms [4]. In addition, the clinician might suspect the severe cutaneous reaction referred to as EMPACT syndrome (erythema multiforme associated with phenytoin and cranial radiation therapy) in oncology patients who are concurrently receiving treatment with phenytoin and cranial radiotherapy for their brain tumor [5].

Drug eruptions can occur from medications that are given in the emergency room immediately before admission. For example, phytonadione (vitamin K1) injection can produce early or later onset, localized or diffuse skin reactions [6]. The administration of these medicines in a hospitalized patient with a new skin rash should be considered; an electronic drug calendar — which includes all medications received by the patient not only after admission but also while in the emergency room — would assist in the discovery of the causative drug.

Preoperative, intraoperative, and postoperative topically administered medications — potentially unsuspected as the culprit of a drug rash — would also be identified in the electronic drug calendar. Disinfectants, such as chlorhexidine and povidone-iodine, that are used to cleanse the skin before surgery can cause contact dermatitis [7]. Open wounds may have been irrigated with neomycin to decrease the possibility of infection may subsequently be associated with a cryptogenic drug rash; the use of this medication may not have been written on the procedure forms [8]. Also, topical antibiotics following surgery can be occult etiologies for skin rashes [7, 9].

Prior hospitalization drug history

One can view records of drug calendars from previous hospitalizations for comparison to narrow the list of agents suspected of causing a hypersensitivity reaction or confirmation of a drug allergy not previously realized. This might be referred to as the inadvertent or accidental drug challenge. It is important to recognize drug allergy because it may be associated with visceral or systemic hypersensitivity reactions and because of

the morbidity and mortality from allergic reactions on subsequent exposure.

Review of previous electronic drug calendars, especially in oncology patients, allows for recognition of drug hypersensitivity reactions potentiated by prior immunotherapy. Immune checkpoint inhibition by ipilimumab may predispose patients to hypersensitivity skin reactions with vemurafenib [10]. In addition, an activated immune response by anti-PD-1 antibody inhibition before either vemurafenib or ipilimumab might result in increased drug toxicity [11].

Drug-related laboratory abnormalities

Certain medications may be more commonly associated with a laboratory abnormality. Therefore, they are more likely to be the culprit drug in hospitalized patients with a new skin rash and accompanying abnormal laboratory studies. Hence, the use of the electronic drug calendar may be of benefit to clinicians under these circumstances when they encounter patients with drug reactions or adverse cutaneous side effects or both.

The drug calendar can be linked to a graphic display of the patient's temperature, complete blood cell count including eosinophils, platelets, and neutrophils, and serum chemistries. This would allow early detection of eosinophilia, thrombocytopenia, leukopenia, elevated liver enzymes (suggestive of hepatitis), and elevated renal function studies (indicative of acute kidney failure). All of these changes can serve as clues to the temporal diagnosis of drug hypersensitivity.

Drug dosage changes

The drug calendar would also include the start and stoppage of medications and the change of dosage of medications. Stevens-Johnson syndrome and toxic epidermal necrolysis are well known to develop with a rapid escalation of the dose of lamotrigine (Lamictal), [12, 13]. In addition, the co-administration of certain medications, such as valproate and lamotrigine, increases the risk of hypersensitivity reaction to lamotrigine [13, 14].

Generic and brand drug names

An electronic drug calendar would make apparent not only brand names but also their generic names so that an allergen is not disguised or hidden in a combination medication. The itemization of the drugs in the calendar could also provide alerts to potential cross-reactions between medications such as penicillin and cephalosporins and between phenytoin, carbamazepine, and phenobarbital [15, 16]. Indeed, future drug calendars might include pharmacogenomic biomarkers for the patient that suggests a genetic predisposition to severe adverse drug reactions such as HLA-B*15:02 (and carriers of HLA-A*31:01) and carbamazepine or HLA-B*57:01 and abacavir [17, 18].

Virus-related drug reactions

Several underlying viral diseases can increase the risk of drug hypersensitivity reactions. These include Epstein-Barr virus (EBV) and ampicillin, HIV and trimethoprim-sulfamethoxazole, and human herpesvirus (HHV)-6, HHV-7, EBV, and cytomegalovirus and the multitude of medications associated with drug rash eosinophilia and systemic symptoms (DRESS), [19-21]. The electronic drug calendar could highlight the medications that are associated with potential virus-related drug reactions.

Look-alike and sound-alike drugs

Lamictal (lamotrigine) and Lamisil (terbinafine) are found very close together on an alphabetical list of medications prescribed electronically and could be easily confused or accidentally typed into the electronic prescription pad. The high dosage of Lamictal 250mg per day, instead of Lamisil 250mg per day for tinea pedis, can result in Stevens-Johnson syndrome [22]. Therefore, it is helpful to have the patient or their family to bring in the pill bottles of medications to confirm they are the correct medications and that there was no pharmacy or prescribing error related to a look-alike (orthographic) or sound-alike (phonetic) similarity between drug names [23].

Drug eruption clinical mimics

Immunocompromised patients may have morbilliform eruptions that morphologically mimic a drug hypersensitivity reaction. Bone marrow transplant patients may have either a viral illness, lymphocyte recovery eruption, or acute graft-versus host disease [24]. Therefore, even with the aid of an

electronic drug calendar and skin biopsy, establishing a definitive diagnosis of drug rash and determining which medication is responsible may be impossible when a drug rash is suspected in these individuals.

Drug rash onset

One rule commonly used by many clinicians, "last on, first off" refers to the most recently added medication is the most likely cause of the drug eruption and should be stopped first. Most drugs typically produce a rash from days to two weeks after onset. In contrast, allopurinol and anti-seizure medications can take four to six weeks to elicit an adverse cutaneous reaction after initiation of therapy. The electronic drug calendar would accurately provide the starting date of all medications.

Concurrent corticosteroid administration

The reduction of a daily corticosteroid dosage could be related to the onset of a drug eruption that relates to a long standing medication; the hypersensitivity was suppressed by the higher dosage of systemic corticosteroid and subsequently appeared during the tapering process. Hence, administration of systemic corticosteroids would have altered the usual time of onset of the drug rash. However, the taper of a course of systemic corticosteroid would be illustrated in an electronic drug calendar.

Drug rash duration

Once the diagnosis of drug rash has been clinically established, data provided by the electronic drug calendar regarding the potentially suspected drugs and listing the frequencies of these medications causing adverse cutaneous events would be useful for identifying the most likely offending agent. It is important to remember that eruptions continue for several days after a drug is stopped before there is improvement. Also, the time course to resolution may be even longer when the patient's renal or hepatic function is compromised.

Conclusion

The electronic drug calendar could serve as an invaluable tool for the diagnosis of drug hypersensitivity by the dermatology hospitalist or any other clinician as the use of electronic medical records continues to become the standard in medicine.

Potential conflicts of interest

The authors declare no conflicts of interests.

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