EDUCATION IN GASTROENTEROLOGY

Adverse Drug Reactions in Clinical Practice: a Causality Assessment of a Case of Drug-Induced Pancreatitis

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Abstract

Modern therapy has changed the way diseases are controlled and has brought significant benefits. In spite of all the benefits, adverse drug reactions are a common, often preventable, cause of illness, disability and even death. Besides the intrinsic danger associated with the drug, patients might have a particular, unpredictable hypersensitivity to certain drugs, which requires careful monitoring. Different studies have shown that adverse drug reactions related hospital admissions comprise up to 10% of the total number of hospitalizations. Adverse drug reactions can be difficult and sometimes impossible to distinguish from the patient’s disease as they act through the same physiological and pathological pathways. Unrecognized adverse drug reactions inflict health damage, hospital costs and may lead to prolonged hospitalization. The purpose of this paper is to review and clarify some specific terminology and to assess the likelihood that a suspected adverse drug reaction is actually due to a medicine, by outlining the information needed for recognizing an adverse drug reaction and the steps of a causality assessment of a theoretical drug-induced case of pancreatitis.

Keywords

Adverse drug reactions – causality assessment – Naranjo probability score.

Introduction

Adverse drug reactions (ADRs) are a major cause of hospital admission and in-hospital morbidity and have become an important clinical problem and a constant concern of the public health systems. A recent large prospective study has showed that ADRs were responsible for 6.5% of all hospital admissions [1]. A meta-analysis suggested that ADRs were between the fourth and sixth commonest cause of death in the United States in 1994, fatal adverse drug reactions being expected in approximately 0.32% of all hospitalized patients [2]. In different studies, the percentage of patients experiencing an ADR during hospitalization has been reported to range from 1.5 to 35%. The diversity of the results of these studies may be explained by the different definitions of ADRs and by the rigor with which ADRs were sought and detected [3]. Apart from the medical impact, ADRs also have an economic impact. It has been suggested that patients who developed adverse effects during hospitalization, were hospitalised an average of 1.2–3.8 days longer than patients who did not, with a substantial increase of the healthcare costs [4]. Up to 57% of the community acquired ADRs are not being recognized by the attending physician upon hospital admission, leading to inappropriate management of the adverse event, exposure of the patient to additional hazards of the drug and prolonged hospitalization [5].

In order to minimise the suffering of patients from ADRs it is essential, though sometimes difficult, to recognise ADRs and to establish a causal relationship between the drug and the adverse event. There are several step-wise approaches that might be helpful in recognizing and assessing possible drug-related ADRs. Many causality methods have been proposed in order to assess the relationship between a drug and an adverse event in a given patient, ranging from short questionnaires to comprehensive algorithms. The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC), and the Naranjo probability scale are the general accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology [6, 7].

This paper intends to clarify the adverse drug reactions’ terminology that is still causing confusion among healthcare professionals and to describe the appropriate approach for the recognition and attribution of causality using a framework of a theoretical drug-induced case of pancreatitis.
Definitions and classification of ADRs

An adverse drug event or experience is defined as ‘any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’. An adverse event is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it. This distinction is important, for example, in clinical trials in which not all events are drug-related. When this term is used to describe adverse outcomes, physicians should be aware that it is not always possible to impute causality [8, 9].

An adverse drug reaction (ADR) is ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of a physiological function’. An ADR, contrary to an adverse event is characterised by the suspicion of a causal relationship between the drug and the occurrence. This definition underlines the fact that the phenomenon is noxious (differentiating adverse drug reaction from side-effects which can also be beneficial) and that it includes doses prescribed clinically, excluding accidental or deliberate overdose [8, 10].

An unexpected adverse reaction is ‘an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation or expected from characteristics of the drug” [11].

A side effect is ‘any unintended effect of a pharmaceutical product occurring at doses normally used by a patient, which is related to the pharmacological properties of the drug’. This definition was formulated to include side effects that, although not the main aim of the therapy, may be beneficial rather than harmful. For example a β-blocker agent used to treat hypertension may, by β-blockade, also relieve the patient’s angina [9, 11].

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

There is a difference between the terms “serious” and “severe”, which are not synonymous. The term “severe” is used to describe intensity (severity) of an event (as in mild, moderate or severe). The event itself can be of relatively minor medical significance, such as a severe headache. This is not the same as the “serious” which is based on the patient and event outcome [8].

The most common classification of ADRs is the one that distinguishes dose-related (type A – augmented effects of the drug action) and non-dose-related (type B – bizarre reactions) adverse drug reactions. There are other groups in this system of classification but these may also be considered as subclasses or hybrids of type A and B ADRs. These are type C ADRs (chronic reactions, dose- and time-related), type D (delayed reactions, time-related), type E (end of use reactions) and type F (failure of therapy) [9, 12]. The characteristics, some examples and the management of these ADRs are listed in Table I [9, 13-18]. An alternative classification system proposes only 3 major groups of adverse reactions, referred as type A (drug actions), type B (patient reactions) and type C (statistical effects) adverse drug reactions [13].

ADRs’ diagnosis and causality assessment

It might be difficult to establish a clinical diagnosis of drug-induced disease as ADRs tend to mimic any natural occurring disease process. Few drugs produce distinctive and specific physical signs that can be considered without any doubt ADRs (e.g. extrapyramidal disorders). In any case, if the patient is taking drugs, a differential diagnosis should consider the probability of an ADR. Several years ago Irey described, in a very comprehensive manner, the diagnostic problems that might interfere in the evaluation of an ADR and proposed a methodology that is still valid and applicable. When assessing the probability of a suspected ADR, the clinician should always evaluate the following aspects: temporal relationship between the use of the drug and the occurrence of the reaction (time to onset), the differential diagnosis (of causes other than the suspected drug), the selection of the responsible drug on the basis of pattern of the event or by exclusion, dechallenge and rechallenge. The pattern of the adverse event must fit the known pharmacology or allergy pattern of one of the suspected drugs or of chemically or pharmacological related compounds. Detailed information on all these aspects that must be considered when evaluating an ADR is presented in Panel 1 [9, 15, 19].

When evaluating an ADR, one must take into consideration the factors that can predispose patients to adverse reactions. Some ADRs are associated with specific patient and/or drug-related factors. These factors are presented in Table II. Among these factors, the pharmacokinetic and pharmacodynamic profile of a drug might be influenced by disease pathology, physiologic status, concomitant therapy and lifestyle. For example, excessively high or low concentrations of a drug at the site of action may occur as a result of altered pharmacokinetic of the drug (e.g. metabolism, excretion). Concurrent diseases such as renal impairment will lead to drug toxicity for drugs or drug metabolites that are highly dependent on the kidney for removal, if the dose of the drug is not properly adjusted. Likewise, doses of the drugs that undergo hepatic metabolism may also produce toxicity in patients with severe hepatic disease, particularly cirrhosis. Cardiovascular disease such as congestive heart failure may also reduce hepatic blood flow and decrease the clearance of certain drugs [20].

Drug-drug interactions contribute to a significant number of ADRs, especially in elderly patients and in patients that are under polymedication. There is an exponential relationship between the number of drugs taken and the probability of an
Adverse drug reactions in clinical practice

Table 1. The classification of adverse drug reaction

<table>
<thead>
<tr>
<th>Type of ADR</th>
<th>Characteristics</th>
<th>Examples</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A (augmented)</td>
<td>Dose-related</td>
<td>Drug toxicity</td>
<td>Reduce dose or withhold</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Nephrotoxicity caused by aminoglycosides</td>
<td>Consider effects of concomitant therapy</td>
</tr>
<tr>
<td></td>
<td>Suggestive time relationship</td>
<td>Dysrhythmia caused by digoxin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Predictable from pharmacological action of the drug</td>
<td>Side effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variable severity, but usually mild</td>
<td>Constipation caused by chronic opioid use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High morbidity</td>
<td>Anticholinergic effects of tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low mortality</td>
<td>They derive from:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reproducible</td>
<td>Primary pharmacology (augmentation of known actions): β-blocker induced bradycardia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Secondary pharmacology (involves different organ or system, but explainable from known pharmacology): β-blocker induced bronchospasm</td>
<td></td>
</tr>
<tr>
<td>Type B (bizarre)</td>
<td>Not dose-related</td>
<td>Intolerance</td>
<td>Withhold and avoid in the future</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tinnitus caused by small doses of aspirin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not related to a pharmacological action of the drug</td>
<td>Allergy (hypersensitivity or immunological)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not predictable from known pharmacology</td>
<td>Result of an immune response to a drug: Penicillin-induced urticaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variable severity, proportionately more severe than type A</td>
<td>Pseudoallergic (non-immunological)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High morbidity</td>
<td>Immediate, generalised reaction involving mast-cell mediator release: respiratory syndromes caused by NSAIDs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High mortality</td>
<td>Idiosyncratic (unexpected response to a drug, not related to an allergic mechanism)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not reproducible</td>
<td>Anticonvulsant hypersensitivity syndrome reaction</td>
<td></td>
</tr>
<tr>
<td>Type C (chronic)</td>
<td>Uncommon</td>
<td>Hypothalamic-pituitary-adrenal axis suppression</td>
<td>Reduce dose or withhold; withdrawal may have to be prolonged</td>
</tr>
<tr>
<td></td>
<td>Related to cumulative dose</td>
<td>by corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long term exposure required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type D (delayed)</td>
<td>Uncommon</td>
<td>Teratogenesis</td>
<td>Often intractable</td>
</tr>
<tr>
<td></td>
<td>Usually dose-related</td>
<td>Carcinogenesis</td>
<td></td>
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<tr>
<td></td>
<td>Seen on prolonged exposure to a drug or exposure at a critical time</td>
<td>Tardive dyskinesia caused by antipsychotic medication</td>
<td></td>
</tr>
<tr>
<td>Type E (end of use)</td>
<td>Uncommon</td>
<td>Opiate withdrawal syndrome</td>
<td>Reintroduce and withdraw slowly</td>
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<tr>
<td></td>
<td>Occurs soon after withdrawal of a drug</td>
<td>Rebound hypotension on clonidine withdrawal</td>
<td></td>
</tr>
<tr>
<td>Type F (failure of therapy)</td>
<td>Common</td>
<td>Ineffectiveness</td>
<td>Increase dosage or change the therapeutic agent; Consider effects of concomitant therapy</td>
</tr>
<tr>
<td></td>
<td>May be dose-related</td>
<td>Resistance of a micro-organism or tumour to the drug action</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often caused by drug interactions</td>
<td>Tolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachyphylaxis</td>
<td></td>
</tr>
</tbody>
</table>

ADR, independent of the therapeutic class and the patient’s underlying disease [21]. Drug interactions may cause altered drug bioavailability, distribution, clearance and additive or antagonistic pharmacodynamic effects. A recently published study indicated that the percentage of drug-drug interactions identified as cause of ADRs was 15% [22]. Another study that investigated potential drug interactions concluded that 68-70% of the potential interactions detected might demand clinical attention, while 1-2% are life-threatening [23]. These interactions have been extensively reviewed in different studies and are often predictable and preventable.

In appropriate prescription of drugs in the elderly population is also a major risk factor for presenting ADRs although incorrectly used drugs constitute a cause of ADRs in the general population too [22, 24]. A recent prospective study demonstrated that from the total number of drugs used by the study population, 26% were incorrectly used and that 44.5% of the ADRs detected involved at least one incorrectly used drug [25]. Unknown co-medication to the treating physician, including self-medication, may compromise drug safety, by increasing the risk of duplicate therapy, drug interactions, and ADRs that are not recognised as such [26]. Thus, it is essential to interview the patient in order to take a proper full drug history and to consider a drug-related cause for the patient’s condition especially when other causes do not explain it. All these factors that might predispose patients to ADR must be taken into consideration when evaluating an adverse event.

The development of a symptom or detrimental outcome while under therapy with several drugs, does not establish the fact that one of the drugs might be the cause of the injury. Likewise, the development of an adverse event or disease, with no relevant time relationship with the use of a drug does not exonerate the drug from being the causative agent. In any case, the failure to recognise an adverse drug reaction, may lead to inappropriate measures. The universal decision to treat an unrecognised drug-related symptom with another medication exposes the patient to additional drug hazards. In
order to avoid multiple drug events, adverse drug reactions recognition is mandatory, as in this case, the appropriate action is the dose reduction or even the discontinuation of the causative drug. Determining if an adverse event is caused by a certain drug with reasonable certainty is a difficult part of ADRs’ evaluation, but it is essential for proper clinical decisions [27, 28].

The aim of the causality assessment is to establish a level of probability regarding the suspicion that a certain drug is responsible for an adverse event. According to the most widely used with or without score algorithms, ADRs can be “certain”, “probable/likely”, “possible” and “unlikely/doubtful”. The WHO-UMC developed a causality system which takes into account the clinical-pharmacological aspects, whereas previous knowledge of the ADR plays a less prominent role [6]. Perhaps the most commonly used causality assessment method, which has gained popularity among clinicians because of its simplicity, is the Naranjo probability scale presented in Panel 2. It is a structured, transparent, consistent and easy to apply assessment method [15].

Causality assessment of a theoretical drug-induced case of pancreatitis

A 56-year old female with a history of hypertension, heart failure and type 2 diabetes mellitus was admitted to an internal medicine department presenting abdominal pain radiating to the back, nausea and vomiting, jaundice, anorexia, sweating, weakness, headache and low-grade fever (38.7°C) for the previous 3 days. The patient’s therapy in the last six months included digoxin 0.25 mg daily except on Thursdays and Sundays, hydrochlorothiazide 25 mg once daily and a combination of rosiglitazone/metformin 1mg/500 mg. Two months prior to admission alfacalcidol 2μg and calcium 1000 mg daily were initiated for osteoporosis prophylaxis. There was no history of alcohol ingestion or previous abdominal surgery.

On physical examination, the abdomen was distended and with diminished bowel sounds. On admission the laboratory data revealed increased serum levels of amylase 549 U/L, glucose 166 mg/dL, WBC 14,400, bilirubin 4.2 mg/dL. Except a calcium value of 12 mg/dL, all other laboratory examinations were normal. Abdominal ultrasonography showed pancreatic oedema and ruled out gallstones, cysts and intestinal obstruction. No biliary dilatation was observed. Drug-induced pancreatitis was considered after exclusion of other causes (alcohol intake, cholelithiasis, hyperlipidemia, abdominal trauma). Hydrochlorothiazide was the suspected drug and it was discontinued. A mild drug induced hypercalcemia was also considered, alfacalcidol and calcium being stopped until the serum levels became normocalcemic. The patient received symptomatic medical treatment. The clinical status of the patient improved within 48 hours after the discontinuation of hydrochlorothiazide. On hospital day 3 serum amylase levels returned to normal and on day 5 the patient was discharged.

Case discussion

Thiazide diuretics in normal doses have been reported to be associated with pancreatitis which develops within
two weeks to as long as 1 year after initiation of the therapy. Several potential mechanisms of thiazide-induced pancreatitis have been suggested in the literature. Thiazides can cause hypercalcemia by decreasing renal calcium excretion. Hypercalcemia is a condition known to increase the risk of pancreatitis which may lead to calculi within the pancreatic duct and/or may accelerate the conversion of trypsinogen to trypsin [20]. At the same time, hypercalcemia is a predominant adverse effect associated with alfacalcidol, which in this patient has been administered in a high dose; the effect usually reverses rapidly on withdrawal of the drug. A probable drug-drug interaction may also be suspected to have increased the calcium serum levels, as the concurrent use of calcium-containing preparations and thiazide diuretics enhance the risk of hypercalcemia. Another drug interaction, with no relation to pancreatitis, but which should be underlined and considered in this case, is digoxin – hydrochlorothiazide interaction which may lead to digitalis toxicity with nausea, vomiting and arrhythmias. If a digitalis glycoside and a thiazide diuretic are used concurrently, the patient should be monitored for ECG signs of potassium depletion, and potassium supplementation should be considered. The causality assessment of this adverse event, presented in Panel 3, revealed a probable association between hydrochlorothiazide and pancreatitis as rechallenge was not performed. In a drug-induced pancreatitis case, patients should never be rechallenged with any drug that has caused even one episode of pancreatitis [20].

**Conclusions**

Prompt recognition of adverse drug reactions, adequate and effective clinical management of their outcome
is mandatory in promoting patients’ safety. Health professionals who care for patients’ drug therapy are taught to consider as well the benefit as the risk when making therapeutic choices. The training regarding adverse events is often limited, considering the reality that expected (due to pharmacologic action) or unexpected (due to idiosyncratic reactions) adverse drug reactions, if not recognised, can increase the risk of harm. Several aspects should be taken into consideration in order to recognize and properly manage adverse drug reactions. The first is that careful observation and high clinical suspicion are of crucial importance in order to identify a drug related problem, including adverse drug reactions. The second is that, even though a drug has been on the market for several years, is widely used and with known side effects profile, unusual adverse reactions may still be identified. Taking into account all these aspects will lead to better adverse drug reaction management and increased patients’ safety.

Conflicts of interest

None to declare.

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