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State of the art

Drug-induced hemolytic anemia: Pharmacological aspects

Anémies hémolytiques médicamenteuses: aspects pharmacologiques

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Résumé

Les anémies hémolytiques médicamenteuses sont des événements indésirables très rares mais potentiellement mortels. On distingue plusieurs formes: stress oxydatif envers des érythrocytes fragilisés (déficit en glucose-6-phosphate déshydrogénase), microangiopathies thrombotiques ou anémies hémolytiques immunes. Différents médicaments susceptibles d'induire chacune de ces formes sont recensés. Lorsqu'un diagnostic d'anémie hémolytique médicamenteuse est évoqué, il est indispensable de procéder à une analyse structurée de l'imputabilité d'un ou de plusieurs médicament(s) en fonction du déroulement chronologique, des données épidémiologiques, des données objectives (lorsqu'on peut en obtenir), et de l'exploration du diagnostic différentiel non médicamenteux. Pour les anémies hémolytiques immunes, il faut confier les investigations à un laboratoire expert, car il s'agit d'un domaine hautement complexe. Si on acquiert la conviction raisonnable qu'on fait face à un événement indésirable médicamenteux, l'arrêt immédiat du ou des médicament(s) incriminé(s) est nécessaire et on peut discuter l'indication à une corticothérapie. Le pharmacologue clinique apporte ses compétences aussi bien pour l'évaluation du possible événement indésirable que pour l'annonce au système de pharmacovigilance, dernière étape, importante, de la démarche.

Mots clés : Anémie hémolytique ; Effet indésirable médicamenteux ; Réaction d'hypersensibilité ; Pharmacovigilance

Abstract

Drug-induced hemolytic anemia is a very rare but potentially lethal adverse drug reaction, which can take the form of oxidative damage to vulnerable erythrocytes (as in glucose-6-phosphate dehydrogenase deficiency), drug-induced thrombotic microangiopathy, or immune-mediated hemolytic anemia. For each form, distinctive drugs are documented as potential triggers. When a formal diagnosis of hemolytic anemia is made following drug administration, a structured approach is recommended to assess the plausibility of an adverse drug reaction based on chronological sequence, epidemiological data, objective evidence (when available), and ruling out of non-drug causes. For suspicions of immune-mediated hemolytic anemia, investigations by a laboratory with specific expertise are crucial given the complexity of the field. If there is good reason to believe hemolytic anemia is drug-induced, immediate drug discontinuation is necessary and corticosteroid administration can be considered. The clinical pharmacology specialist can support evaluation of drug imputability and report the case to the pharmacovigilance system, an important last step in managing such events.

Keywords: Anemia hemolytic; Drug-related side effects and adverse reactions; Drug hypersensitivity; Pharmacovigilance

1. Introduction

Drugs may seldom cause Hemolytic Anemia (HA). Although very rare, it is essential to recognize this Adverse Drug Reaction

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(ADR), since timely drug cessation can prevent a potentially fatal issue. The range of drugs and mechanisms involved are still only partially understood; significant progress has been made in the previous decades, but it remains a challenging field due to potential confounding factors and the complexity of the immune system's working. This article is a narrative review based on recent articles (2010–2016, and a 2004 review).

2. Epidemiology

The incidence of Drug-Induced Hemolytic Anemia (DIHA) is approximately 1 per million/year. Reliable quantitative data are missing, though, since traditional study designs often don't capture, let alone quantify, such rare events. Hence, case reports and pharmacovigilance reports are the only source of relevant data. Some such reactions are likely to go undiagnosed or misdiagnosed, given the potential non-drug confounding factors and the difficulty to identify the culprit when, as is often the case, the patient has been exposed to several suspected drugs in the same time window.

3. Pathophysiology and main drugs involved

DIHA is a hypersensitivity reaction, i.e. an ADR, which is unrelated to pharmacological activity (also called idiosyncratic). It is traditionally described as dose-independent, but this is only partially true, because longer or more intense drug exposure is a well-known risk factor for all ADRs, including hypersensitivity.

DIHA may be immune or non-immune.

Non-immune DIHA occurs when oxidative-stress-susceptible Red Blood Cells (RBCs) meet drugs causing oxidative damage, either in themselves or through oxidizing metabolites or through oxygen-radicals-producing metabolism. Glucose-6-Phosphate (G6PD) Deficiency, with RBCs' failing ability to regenerate Nicotinamide Adenine Dinucleotide Phosphate (NADP), is the underlying condition most often encountered in such situations. It affects an estimated 400 million people worldwide, predominantly from Africa, the Middle East, and Southeast Asia. It can be diagnosed by different screening tests and by measuring enzyme activity.

The majority of individuals is asymptomatic, but may develop episodes of acute hemolysis triggered by medications, certain foods, and infections. Rarely, individuals with severe disease may have chronic hemolysis.

Many drugs have been involved, but causality is difficult to designate, particularly for antibiotics where infection is a major confounding factor. Drugs to be avoided include dapsone, primaquine, sulfanilamide, nitrofurantoin and rasburicase [1]. Rasburicase-induced hemolytic anemia in pediatric patients has been recently reviewed [2].

Syndromes of Thrombotic Microangiopathy (TMA), including thrombocytopenic purpura and hemolytic-uremic syndrome, also can be drug-induced. Drugs most frequently suspected, with strong cumulative evidence but no certainty of causality, are antineoplastic, immunosuppressant or antiplatelet agents, as well as quinine/quinidine [3]. For almost all drugs, mechanism of this ADR is poorly understood. Direct or immune injury to endothelial cells has been established for some drugs. A systematic review of drug-induced TMA reports has been recently published [4].

Immune DIHA is classified as a type 2 reaction in the Gell and Coombs classification of hypersensitivity reactions, i.e. cytotoxic, antibody-dependent, mediated by immunoglobulin (Ig) G or M or by complement.

Hence, following a first exposure, several days are needed to develop the kind of immune response which can induce DIHA. In case of a re-exposure, DIHA can happen immediately. Exceptionally, it may also happen in the course of a long-term, continuous exposure.

Larger drugs with more complex structures and those that tend to undergo haptenization are more likely to be immunogenic. Intravenous and intramuscular administrations are at higher risk than oral or inhaled routes. In patients with cystic fibrosis, reduced lung function, advancing age and greater cumulative exposure are thought to be risk factors for hypersensitivity to beta-lactams [5].

Criteria for "indisputable evidence" of a drug being a cause of immune DIHA have been proposed by long-time researchers who regularly publish updates in this field. Antibiotics, particularly penicillins and cephalosporins, and non-steroidal anti-inflammatory drugs are frequent causes of DIHA, but many other drugs can be involved. A comprehensive list is available in a recent review, structured according to the three main postulated mechanisms that are drug-dependent antibodies, drug-independent antibodies, and non-immunologic drug absorption. In the experience of those authors, piperacillin is now the most frequently encountered cause of immune DIHA, while increasing data point to transplant-associated and chemotherapeutic drugs (including both "standard" drugs and monoclonal antibodies) as a cause of immune DIHA [6]. Recent, well-documented case reports give further insight into piperacillin- and ceftriaxone-induced hemolytic anemia [7–9].

At the Charité Institute for Transfusion in Berlin, a retrospective review of immune DIHA over 20 years identified 73 patients with DIHA related to 15 different drugs. The most common drugs involved were diclofenac ($n = 23$), piperacillin ($n = 13$), ceftriaxone ($n = 12$) and oxaliplatin ($n = 10$). Hemolysis was acute in all patients, complicated by transitory renal and/or liver failure or shock in 11 patients; 17 patients died (23%) [10]. Table 1 summarizes known mechanisms and drugs involved in DIHA.

4. Clinical features and management

A DIHA case report by Raffray L et al. [11] will be taken here as an example of diagnostic and therapeutic management. It is briefly summarized as follows: A 17-year African female was diagnosed with *Plasmodium falciparum* infection. She initially presented with a low-normal hemoglobin level (Hb) (12.6 g/dL, reference range 12–16 g/dL) with elevated lactate dehydrogenase (LDH) and total bilirubin, and low haptoglobin, indicative of hemolysis. She was treated with oral artemether/lumefantrin. On the following day, septic shock led to intensive care management with a switch to intravenous arte-