Kruczyńska-Kisły Violetta, Fabian-Danielewska Anna, Fabian Wiesława. Drug Nephrotoxicity in Family Doctor Practice. Journal of Education, Health and Sport. 2019;9(1):207-210. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2547107
http://ojs.ukw.edu.pl/index.php/johs/article/view/6509

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 03.01.2019. Revised: 11.01.2019. Accepted: 23.01.2019.

Drug Nephrotoxicity in Family Doctor Practice

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Summary

Drug Nephrotoxicity is a frequent and growing phenomenon. It is reported that up to 20% of episodes of acute renal failure are due to medication. In the practice of the family doctor, the problem of drug nephrotoxicity is significant. The family physicians are dealing with an aging population of patients with cardiovascular diseases, diabetes, circulatory insufficiency, and pre-existing renal function. This group of patients is subjected to many diagnostic and therapeutic procedures that may worsen the function of kidneys, and often use numerous drugs, and abuse analgesics. Most drugs that cause kidney damage work through such mechanisms: disorder of intra-glomerular hemodynamics, direct damage to the kidney tubules, an inflammatory process, nephropathy associated with the formation of crystals, rhabdomyolysis, thrombotic microangiopathy. Most cases of drug-induced kidney damage are reversible as long as it is diagnosed early and the factor responsible for damage is eliminated.

Keywords: nephrotoxicity; drugs; renal function

Introduction

Nephrotoxicity is defined as dysfunction or kidney disease resulting from the direct or indirect action of drugs or industrial / environmental chemical agents [1].

Drug Nephrotoxicity is a frequent and growing phenomenon. Although drug renal failure is often reversible after discontinuation of harmful therapy, it is associated with hospitalization and costly medical care [2]. It is reported that up to 20% of episodes of acute renal failure are due to medication [3-5]. In the practice of a family doctor, the problem of drug nephrotoxicity is of great importance for several reasons listed below. First of all, the family physician is dealing with an aging population of patients with cardiovascular diseases, diabetes, circulatory insufficiency, and pre-existing renal function (glomerular filtration rate

GFR <60 ml / min / 1.73 m^2 body surface). Secondly, this group of patients is increasingly subjected to numerous diagnostic and therapeutic procedures that potentially may worsen the function of the kidneys (eg imaging examinations using radiological shading agents) [6]. Thirdly, patients over 60 years old often use numerous drugs (polypragmagia), and abuse analgesics (and in particular, non-steroidal anti-inflammatory drugs available without a prescription). In addition, in this group of patients there may be diseases that aggravate hydration (eg diarrhea, forced diuresis and insufficient intake of fluids). All these factors make the elderly population particularly vulnerable to nephrotoxic effects of drugs.

Risk factors

Knowledge of risk factors and pathomechanisms of drug-induced kidney damage is crucial for the diagnosis and prevention of nephrotoxicity [1]. Risk factors can be divided into internal (related to the patient) and external (related to the properties of the drug). The factors related to the patient include the following: age over 60, previous kidney damage (GFR <60 ml / min / 1.73 m2), and co-morbidities (diabetes, hypertension, circulatory insufficiency, systemic lupus, cirrhosis, dehydration, diarrhea, acidosis, hypokalemia, hyperuricemia and others). Factors related to drug properties include potential nephrotoxicity of certain substances (eg. aminoglycosides, amphotericin B, cisplatin, radiographic contrast agents), prolonged use, frequency and form of drug administration, as well as drug interactions (e.g., use of contrast agents with potentially nephrotoxicity) drug).

Pathomechanism

Most drugs that cause kidney damage work through one or more of the following mechanisms at the same time:

- disorder of intra-glomerular hemodynamics
- direct damage to the kidney tubules
- an inflammatory process
- nephropathy associated with the formation of crystals
- rhabdomyolysis
- thrombotic microangiopathy

Intrahepatic hemodynamic disorders

In a healthy, adult human, about 120 ml of plasma is filtered in a glomerulus in one minute (GFR). Perfusion depends on the pressure in the afferent and efferent arteriole, which are subject to vasodilatation or vasoconstriction due to circulating prostaglandins and angiotensin. Since glomerular pressure determines glomerular filtration (GFR), it would seem that small changes in pressure could cause large fluctuations in GFR. However, GFR remains almost constant over a wide range of fluctuating pressure in the delivery artery. This mechanism is called autoregulation.

Drugs that affect the level of prostaglandins (eg, non-steroidal anti-inflammatory drugs) and angiotensin activity (e.g., convertase blockers and angiotensin receptor blockers) can interfere with the autoregulation mechanism and lead to a reduction in GFR. Other drugs, in turn, directly cause dose-dependent vasoconstriction afferent and efferent arterioles affecting the reduction of GFR (eg cyclosporine).

In conclusion, both non-steroidal anti-inflammatory drugs, convertase blockers (captopril, enalapril, ramipril) and angiotensin receptor blockers (eg candesartan, losartan, valsartan) [7,8] and cyclosporin may potentially interfere with intra-glomerular haemodynamics and reduce GFR [9].

Direct damage to the kidney tubules

Renal coils due to their role in reabsorbing and exposure to high levels of potential toxins are susceptible to damage. Drugs that cause direct damage to the coils can cause damage to mitochondrial functions, disrupt coil transport and form free radicals [10,11]. Drugs that work in this mechanism include aminoglycosides, amphotericin B, cisplatin and some antiviral drugs.

The inflammatory process

Some drugs can cause an inflammatory process in the glomeruli, renal tubules and surrounding interstitial cells. The inflammatory process leads to fibrosis and scarring. Glomerulonephritis is an inflammatory process that is often accompanied by proteinuria. Drugs that can cause such changes include gold salts, hydralazine, penicillamine, interferon, lithium, non-steroidal anti-inflammatory drugs and propylthiouracil.

Interstitial nephritis is an immune-mediated inflammatory process. Drugs that cause interstitial inflammation combine with the antigen in the kidneys and induce an immune response. However, classic hypersensitivity symptoms such as fever, rash or eosinophilia are often absent [11] and the onset of the disease may be secretive. Many medications can cause both acute chronic interstitial nephritis. According to Czekalski, drugs are responsible for about 30% of cases of acute interstitial inflammation [12]. It is most often caused by non-steroidal anti-inflammatory drugs (ibuprofen, indometacin, naproxen, piroxicam) and antibiotics (ampicillin, penicillin, erythromycin, tetracyclines and sulfonamides). Chronic inflammation is characterized by latent onset and lack of hypersensitivity symptoms. Chronic inflammation can be caused by aspirin, acetaminophen and non-steroidal anti-inflammatory drugs, used chronically at high doses (> 1 gram daily for more than two years), especially in patients with co-existing kidney disease [13,14].

Nephropathy associated with the formation of crystals

Damage to kidney function can also be associated with the use of drugs that form urine-insoluble crystals. These crystals make it difficult to urinate and also cause reactions in the interstitium. The probability of crystals precipitation depends on the concentration of the drug in the urine, and the pH of the urine. The most exposed to this phenomenon are dehydrated patients who already have kidney failure. Also, chemotherapy and elevated levels of uric acid and calcium phosphate may be associated with kidney damage in this mechanism. Drugs that damage the kidneys in this mechanism include ampicillin, cpirofloxacin, sulfonamides, aciclovir and methotrexate.

Rhabdomyolysis

Rhabdomyolysis is a clinical condition resulting from the release of transverse striated muscle cells into the bloodstream as a result of damage to their cell membranes [12]. As a result of this phenomenon, plasma myoglobin appears and creatine kinase increases. Myoglobin induces kidney damage by direct toxicity, renal tubular obstruction and GFR lesions. Statins are the most recognizable group of drugs that can cause rhabdomyolysis, however, it occurs relatively rarely in the case of statin monotherapy (0.44 / 10,000 patients per year of therapy) [15]. Many other drugs and substances can also cause rhabdomyolysis (fibrates, colchicine, barbiturates, cocaine, heroin, caffeine, carbon monoxide and acetylsalicylic acid).

Thrombotic microangiopathy

Thrombotic microangiopathy causes kidney damage due to platelet clots in the microcirculation. The mechanism of kidney damage is associated in this case with both an immunological reaction and direct toxicity. Drugs that can damage the kidneys in this mechanism include clopidogrel, ticlopidine, and cyclosporine.

Prevention

Most cases of drug-induced kidney damage are reversible as long as it is diagnosed early and the factor responsible for damage is eliminated [16]. In high-risk patients, the initial function of the kidneys should be determined and closely monitored during therapy. There are smartphone applications that allow you to easily determine the GFR. The US Food and Drug Administration (FDA) recommends using the Cockcroft-Gault formula in adult patients because this pattern has been used in most pharmacokinetic studies [17]. This formula should be used when using drugs whose dosage depends on kidney function [12]. Another important method that can minimize the risk of drug-induced kidney damage is to adjust the dosage of the drug depending on the kidney function (GFR). Also important is knowledge of drugs (and other substances) that may be nephrotoxic and avoid the use of a combination of such drugs / substances. It is also important to educate the patient about the appropriate hydration during treatment with drugs that may impair renal function

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