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Original Research Article

The influence of oxazaphosphorine agents on kidney function in rats

Łukasz Dobrek [a,*], Beata Skowron [a], Agnieszka Baranowska [a], Klaudia Płoszaj [b], Dorota Bądziul [c], Piotr Thor [a,c]

[a] Department of Pathophysiology, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
[b] Medical analytics graduate student, Jagiellonian University Medical College, Krakow, Poland
[c] Department of Human Physiology and Pathophysiology, Faculty of Medicine, University of Rzeszów, Rzeszow, Poland

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ABSTRACT

Background and objective: The application of cytostatic oxazaphosphorines such as cyclophosphamide (CP) and ifosfamide (IF) is associated with the risk of kidney damage that, depending on the type of drug, dose and route of administration, adopts a different clinical entity and severity. The aim of our study was to assess the influence of CP and IF on the kidney histology and function in rats intraperitoneally treated with four doses of either CP or IF.

Materials and methods: A total of 30 rats were divided into three groups (10 in each group): group 1 (control), sham treated with saline solution, group 2 (treated with 75 mg/kg b.w. of CP), and group 3 (treated with 60 mg/kg b.w. of IF). After the treatment rats were sacrificed, blood was collected and nephrectomy and cystectomy were performed. Qualitative and quantitative parameters (including neutrophil gelatinase-associated lipocalin-1, NGAL-1) of kidney function were assayed in urine and plasma.

Results: CP-treated rats were characterized by a significant polyuria, decreased urine pH and by decreased daily urinary excretion of sodium, potassium, urea and uric acid accompanied by increased NGAL-1 excretion. A significant decrease of the plasma uric acid concentration was also observed. IF-treated animals were also characterized by decreased urine pH but with normal daily urinary excretion of assessed substances (except for reduced uric acid excretion).

Both CP and IF treated rats did not show any histopathological abnormalities in their kidneys.

Conclusions: CP caused more advanced kidney dysfunction and some indices suggested the development of prerenal acute kidney injury. In the CP-treated group some particularly marked urinary and plasma uric acid disturbances suggested compensation of increased oxidative stress as uric acid is considered to exert also antioxidant properties.

* *Corresponding author at*: Department of Pathophysiology, Faculty of Medicine, Jagiellonian University Medical College, Czysta 18, 31-121 Krakow, Poland.
E-mail address: lukaszd@mp.pl (Ł. Dobrek).
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1. Introduction

Nephrotoxicity is defined as a structural and/or functional kidney damage resulting from exposure to any noxious factor of toxic or ischemic character. Drugs are one of kidney-affecting agents, therefore the incidence of drug-induced nephrotoxicity has been continuously increasing [1]. Some general issues determining drug-induced kidney disease include glomerular or tubular dysfunction, impairment of renal blood flow or disturbances of kidney metabolic and endocrine function, accompanied by microscopic structural lesions or gross morphological changes [2]. The background for nephrotoxicity are detailed pathomechanisms, affecting renal vasculature (e.g. hemodynamic acute kidney injury or thrombotic microangiopathy), glomeruli (e.g. minimal change disease, focal segmental glomerulosclerosis) or tubulointerstitium (acute tubular necrosis, [ATN], crystal nephropathy or tubulopathies such as Fanconi syndrome, salt wasting, nephrogenic diabetes insipidus, syndrome of inappropriate antidiuresis) [3,4].

Nephrotoxicity remains an important adverse drug reaction (ADR) in case of administration of many classes of pharmacological agents, including particularly: contrast media, immunosuppressants (mostly cyclosporine A), aminoglycosides, sulphonamides, amphotericin B, non-steroidal anti-inflammatory drugs, gold and D-penicillamine, antihypertensives, with special attention to angiotensin converting enzyme inhibitors or diuretics [1]. Also, many cytostatic drugs are characterized by a significant nephrotoxicity. Therefore, despite the improvement in effectiveness of chemotherapy, drug-induced kidney damage remains a complication entangling the entire treatment [3].

Among the chemotherapeutics endowed with nephrotoxicity, oxazaphosphorine alkylating agents should be mentioned. These compounds include cyclophosphamide (CP), ifosfamide and less frequently used trofosfamide. CP is used in chemotherapy of both solid tumors and acute leukemia and is used as an immunosuppressant in nonneoplastic disorders (systemic lupus erythematosus and rheumatoid arthritis). Ifosfamide (IF) is also an effective agent used in treatment of solid tumors, including testicular cancer, rhabdomyosarcoma, Wilms' tumor, Ewing's sarcoma, bone sarcomas, osteosarcoma and neuroblastoma as well as some forms of lymphoma [3,5]. The main ADR of CP is hemorrhagic cystitis, induced by acrolein – a toxic product released during CP biotransformation. Ifosfamide shares with cyclophosphamide a toxic profile characterized by urotoxicity. Moreover, IF is considered to be more nephrotoxic compared to CP [2,3,5]. That is due to the fact that biotransformation of IF leads to a principal release of chloroacetaldehyde that is attributed to exert a more powerful nephrotoxic effect compared to acrolein [6]. To sum up, nephrotoxicity of oxazaphosphorine agents depends on the type of drug (CP vs. IF), the applied dose, the route of administration, the total time of treatment, the presence of other co-existing factors predisposing to nephrotoxicity [2,4]. That multitude of nephrotoxicity-determining factors also results in a varied clinical description of kidney damage evoked by use of those agents. Moreover, published reports of kidney damage evoked by oxazaphosphorine administration are only partial, based on the different nature of the assessment (imaging studies, selected biochemical parameters), so any more complex laboratory analysis of the issue is still missing.

Therefore, the aim of our study was to assess the influence of two oxazaphosphorines (CP and IF) on the renal histology and function, estimated by panel of laboratory parameters assessed in urine and plasma, in rats treated with four successive doses of either CP or IF.

2. Materials and methods

The medical experiment described in this paper was approved by the I Local Ethical Committee in Krakow. The experiment was carried out in accordance with both the Directive 2010/63/EU on the protection of animals used for scientific purposes and with the Polish Act of 15 January 2015 on the protection of animals used for scientific or educational purposes (JL, February 26, 2015, Pos.266).

2.1. *Examined groups of animals and a general plan of the experiment*

The experiment included 30 10-week-old albino Wistar rats, in equal quantities of males and females. Animals were obtained from the Central Animal House of the Faculty of Pharmacy of the UJCM in Krakow.

Upon arrival to the local Animal House of the Department of Pathophysiology of the UJCM, they were kept during the first seven days in an isolated room in order to acclimatize to the new living conditions. After that period, the rats were randomly assigned to the study groups of the same size (10 in each group; 5 males and 5 females): group 1 (control rats), group 2 (rats with CP-induced chronic cystitis), and group 3 (rats with IF-induced chronic cystitis).

All animals survived till the end of the experiment, although the overall condition of the animals from groups 2 and 3 was deteriorating with subsequent CP/IF doses, respectively.

During the experiment (except when rats were housed in individual metabolic cages), animals were kept in single-sex cages separate for the study groups, with unlimited access to water and standard feed (Labofeed, Kcynia, Poland), in the air-conditioned room with a constant temperature and humidity, maintaining a 12/12-h day/night cycle.

The plan of the experiment assumed initial assessment of vital signs, daily diuresis, feed and water consumption of all study animals performed in individual cages. Urine samples were collected over 24 h for subsequent laboratory analysis and for qualitative and semi-quantitative analysis of urine with urine dipsticks. Then, animals in groups 2 and 3 received CP or IF treatment, respectively, to induce chronic cystitis in 7 days. Control individuals were given normal saline. After the last CP/IF/saline dose all animals were once more monitored during 24 h in metabolic cages, with assessment of the same parameters as those before the treatment and urine samples were collected again. After the second stay in metabolic cages, blood samples for further biochemical assay were also collected. Finally, the animals were sacrificed and cystectomy

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