Severe Intoxication with Methotrexate Possibly Associated with Concomitant Use of Proton Pump Inhibitors

RAOUL SANTUCCI[1], DOMINIQUE LEVÊQUE[2], VÉRONIQUE KEMMEL[3], PATRICK LUTZ[4], ANNE-CÉCILE GÉROUT[2], AURÉLIA N'GUYEN[4], AURÉLIE LESCOUTE[1], FRANCIS SCHNEIDER[5], JEAN-PIERRE BERGERAT[1] and RAOUL HERBRECHT[1]

[1]Oncology, [2]Pharmacy, [3]Biology, [4]OncoPaediatrics and [5]Intensive Care Unit, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, 67000 Strasbourg, France

Abstract. *Background: Delayed elimination of methotrexate associated with serious side-effects has been attributed to the co-administration of benzimidazole proton pump inhibitors. Patients and Methods: We have retrospectively analyzed the causes of delayed methotrexate elimination in patients who had received the rescue agent glucarpidase to evaluate the potential implication of benzimidazoles. Results: Between 2002 and 2008, six patients (mean age: 30 years; range: 4-74 years) were treated with glucarpidase. Delayed elimination associated with impaired renal function occured after the first cycle except in 2 patients (2nd and 8th administration of high-dose methotrexate). The possible causes of delayed elimination identified were: insufficient hydration (n=1) and drug–drug interactions (n=5). The potential drug–drug interactions included the co-administration of piperacillin/tazobactam (n=1) and proton pump inhibitors (omeprazole, n=3; esomeprazole, n=2). Impaired elimination of methotrexate was not observed either in the 3 patients who were treated further or during the previous cycles of the 2 pretreated patients in relation to the absence of co-prescription of proton pump inhibitors. Conclusion: In line with the recent literature and given the prohibitive cost of glucarpidase, we have advocated the cessation of proton pump inhibitors administration during methotrexate treatment.*

Methotrexate is an antifolate agent that is used in the treatment of numerous types of cancer and that is primarily eliminated by the kidneys (1). Methotrexate elimination may be delayed by co-administered drugs such as anti-inflammatory drugs, ciprofloxacin and piperacillin (2-4). These pharmacokinetic interactions are possibly due to a reduction of the renal secretion of the antifolate in relation to the blockade of proximal drug transporters (5). Contrary to accepted ideas, it is unlikely that these clinically relevant interactions are imputable to plasma protein displacement because methotrexate is not highly bound to albumin (46%) and has a low hepatic extraction ratio (6). Recently, delayed elimination of methotrexate associated with serious side-effects has been attributed to the co-administration of benzimidazole proton pump inhibitors (omeprazole, pantoprazole, lansoprazole and rabeprazole) (7-12). The possible mechanism of interaction is the inhibition of tubular secretion *via* the luminal transporter breast cancer resistance protein (BCRP also referred to as ABCG2) (13).

Delayed methotrexate elimination is particularly observed in treatments using the antifolate at high dose (*i.e.* >1 g/m^2 intravenously). In such treatments, plasma concentrations of methotrexate are systematically monitored to ensure appropriate elimination and to prevent toxic events and, in particular, nephrotoxicity. Delay in methotrexate elimination is usually defined by plasma levels above 15 μmol/l at 24 hours, ≥1.5 μmol/l at 48 hours and ≥0.15 μmol/l at 72 hours. Various procedures are used to prevent toxic effects of high-dose methotrexate such as hydration (2.5 to 3.5 l/m^2 per day) that promotes the elimination of the drug and urine alkalinization to prevent the risk of intra-tubular precipitation of the parent drug and the metabolite (7-hydroxy-methotrexate). In addition, calcium folinate is added to protect healthy cells. Nevertheless, despite these measures, delayed elimination and acute renal failure may occur. Hence, the incidence of nephrotoxicity was 1.8% in osteosarcoma patients treated by high-dose methotrexate in clinical trials (14). Among these patients, the mortality rate was 4.4% (14). As stated by the authors, the incidence may be higher in clinical practice. Methotrexate intoxication is managed by haemodialysis, haemoperfusion or the administration of glucarpidase (formerly carboxypeptidase

Correspondence to: Dominique Levêque, Pharmacy, Hôpital Hautepierre, avenue Molière, 67000 Strasbourg, France. Tel: +33 0388128213, Fax: +33 0388127804, e-mail: dominique.leveque@chru-strasbourg.fr

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G2), an enzyme that hydrolyses methotrexate in the plasma (15). The main disadvantage of glucarpidase is its prohibitive cost (28 000-35 000€ per injection).

The impact of proton pump inhibitor co-administration on methotrexate elimination has been assessed in a general population of patients treated by the antifolate at high dose (10, 12). The goal of our study was to specifically evaluate the potential implication of co-administered benzimidazoles in patients treated by the rescue agent glucarpidase for severe methotrexate intoxication.

Patients and Methods

We conducted a retrospective non-interventional study on patients treated with glucarpidase due to a delay in elimination of methotrexate, between 2002 and 2008 at the University Hospital of Strasbourg, France. Different risk factors for delayed elimination were investigated: insufficient hydration or alkalinization, co-administration of benzimidazole proton pump inhibitors (*i.e.* those used in our hospital: omeprazole, esomeprazole, pantoprazole and lansoprazole) and recognized drug–drug interactions according to the French Drug Agency. We also looked at the eventual co-prescription of benzimidazoles in patients pretreated or treated further with high dose methotrexate.

Results

Six patients (mean age: 30 years; range: 4-74 years) were identified. Methotrexate was administered intravenously at high dose (mean: 6.34 g/m^2; range: 0.968-12.7 g/m^2) for osteosarcoma (n=3), lymphoma (n=2) and neuroblastoma (n=1). The patients had not been pretreated with high-dose methotrexate except two (1 and 7 previous cycles, respectively). Glucarpidase was administered in a context of delayed elimination of methotrexate (*i.e.* plasma concentration determined by the homogeneous enzyme immunoassay EMIT test ≥15 μmol/l at 24 h, ≥1.5 μmol/l at 48 h and ≥0.15 μmol/l at 72 h) and impaired renal function (serum creatinine >1.5 upper the limit of normal, or the doubling of serum creatinine after the administration of methotrexate). Glucarpidase (45 to 79 UI/kg) was given intravenously 24 to 72 hours after administration of methotrexate in one (n=4) or two (n=2) injections. All patients recovered from adverse events.

The potential causes of delayed elimination of methotrexate were insufficient hydration (n=1) and drug–drug interactions (n=5). The patient with insufficient hydration received only 2 l instead of 3 l/m^2 per day. Potential drug–drug interactions resulted from concomitant administration of esomeprazole (n=2), omeprazole (n=3) and piperacillin/tazobactam (n=1). One patient combined insufficient hydration with co-administration of omeprazole and one patient received both piperacillin/tazobactam and omeprazole. No cause was found for one patient.

After the episode of intoxication, three patients received a new cycle of high-dose methotrexate without proton pump inhibitor. None of these patients presented a second delay in methotrexate elimination. Regarding the two patients pretreated with high-dose methotrexate, no delay in elimination was observed in the previous cycles. Benzimidazoles were not administered in these courses.

Discussion

Methotrexate nephrotoxicity is attributable to the precipitation of the parent drug and the major metabolite in urine and to a direct toxic effect occurring during renal secretion (14). Renal dysfunction leads to increased exposure to methotrexate (delayed elimination) and to other toxicities (myelosuppression, mucositis, hepatitis). Precipitation is prevented by urine alkalinization and hydration, while direct renal toxicity may be prevented by the avoidance of drugs that block the luminal efflux of methotrexate (*i.e.* drugs that enhance renal cell exposure to the antifolate). In our population of six patients treated with glucarpidase for severe intoxication to methotrexate, we have reported one case with a defect of hydration. We also found that five out of six patients had received concomitant drugs that potentially blocked luminal secretion, essentially proton pump inhibitors (omeprazole and esomeprazole). In addition, no delay in elimination was observed during the courses without proton pump inhibitor co-prescription, neither in the three patients who received a further cycle of methotrexate nor in the two pretreated patients with the antifolate at high dose. In line with the literature, a pharmacokinetic interaction between methotrexate and benzimidazoles can be suspected. Interaction between omeprazole and high-dose methotrexate was first reported in 1993 in a patient with osteosarcoma (7). Confirming and conflicting data were then obtained in some case reports involving either omeprazole or pantoprazole (8, 9, 11, 16). The inhibition of renal secretion *via* BCRP as a potential mechanism of interaction was proposed in 2004 (13) and the expression of BCRP in membranes of human renal cells was later reported (17). Larger and more convincing sets of data were obtained in two studies (10, 12). First, Joerger *et al.* (10) examined the factors affecting the clearance of methotrexate and its metabolite 7-hydroxy-methotrexate in 76 patients receiving the antifolate at high dose intravenously. Among these 76 patients, 13 received benzimidazoles (omeprazole or lansoprazole). Co-administration of omeprazole or lansoprazole was associated with a 27% decrease in the clearance of methotrexate and a 39% decrease in the clearance of the metabolite. Similar results were recently found by Suzuki *et al.* (12) in 74 cancer patients treated by high-dose methotrexate. The potential implication of benzimidazoles as a risk factor of impaired elimination was

examined in 171 cycles. Co-administration of proton pump inhibitors (omeprazole, lansoprazole and rabeprazole) was statistically found more frequently (31.7%) in patients with episodes of delayed elimination of methotrexate than in patients with episodes of normal elimination (13.8%).

In conclusion, combining a benzimidazole with high-dose methotrexate may lead to severe intoxication necessitating the use of the antidote glucarpidase. The proton pump inhibitor might block the renal secretion of methotrexate at the luminal side of the proximal cell enhancing the intracellular exposure to the antifolate and, in turn, producing both a toxic effect and increased plasma concentrations. Avoiding the concomitant administration of proton pump inhibitors with high-dose methotrexate may reduce the risk of nephrotoxicity and the use of costly glucarpidase. Given the existence of alternatives to proton pump inhibitors (such as ranitidine), we advocate the cessation of benzimidazole prescriptions for patients receiving high-dose methotrexate.

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