UNIVERSIDADE DE SÃO PAULO
FACULDADE DE CIÊNCIAS FARMACÊUTICAS DE RIBEIRÃO PRETO

Atividade dos transportadores de ânions orgânicos 1 e 3 empregando a farmacocinética da furosemida: impactos da gestação e da pielonefrite aguda

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Ribeirão Preto
2022

RESUMO

BENZI, J. R. L. **Atividade dos transportadores de ânions orgânicos 1 e 3 empregando a farmacocinética da furosemida: impactos da gestação e da pielonefrite aguda**. 2022. 181f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2022.

Os transportadores de ânions orgânicos (OAT) 1 e 3 são de fundamental importância na excreção renal e consequentemente no regime de dosagem de medicamentos. No entanto, pouco se conhece sobre a influência da inflamação associada à infecção renal, principalmente em gestantes, na expressão/atividade dos referidos transportadores. Assim, este estudo desenvolveu protocolos para investigação da inflamação e da gravidez na atividade *in vivo* dos OAT 1 e 3 pela avaliação da farmacocinética do marcador furosemida (FUR). No primeiro protocolo, o impacto da inflamação foi investigado em gestantes diagnosticadas com pielonefrite aguda (modelo de inflamação), nos segundos e terceiros trimestres da gestação. As pacientes foram tratadas com cefuroxima (CER) endovenosa 750 mg TID e receberam dose única oral de FUR 40 mg antes (n = 10) e 40 mg após (n = 7) o término do tratamento com o antibiótico, alta hospitalar e redução da inflamação. As concentrações de citocinas plasmáticas foram avaliadas nas duas etapas deste protocolo. Adicionalmente, buscou-se descrever a farmacocinética e a relação PK-PD da CER contra 3 possíveis MIC para *Escherichia coli* (2, 4 e 8 µg/mL) nesta população. O segundo protocolo deste estudo investigou o impacto da gestação em 10 participantes gestantes saudáveis e 12 participantes não gestantes saudáveis que receberam dose única oral de FUR 40 mg. Em todos os grupos e fases, as amostras seriadas de sangue e urina foram colhidas até 24h após a administração da FUR. Os métodos de quantificação de FUR, glicuronídeo de FUR e CER em matrizes biológicas foram desenvolvidos e validados em LC-MS/MS. A disposição cinética da FUR foi avaliada pelo modelo não compartimental. O impacto da inflamação (antes e após tratamento com CER) na farmacocinética da FUR foi avaliado pelo teste de *Wilcoxon*, enquanto o impacto da gravidez (grávidas e não grávidas) foi avaliado pelo teste de *Mann-Whitney*. O nível de significância foi fixado em 5% para ambos os testes. Os métodos bioanalíticos apresentaram sensibilidade e limites de confiança adequados para estudos de farmacocinética, possibilitando a quantificação de FUR, glicuronídeo de FUR e CER em até 24 h após as doses administradas. Quando comparado ao período pós-infecção/inflamação, as gestantes diagnosticadas com

pielonefrite aguda apresentaram concentrações de citocinas plasmáticas de 2 até 100 vezes maiores para a MCP-1, TNF-α, IFN-γ, IL-6 e de até 10 vezes para a proteína C reativa. Além disso, apresentaram maiores valores medianos (intervalo interquartil) de T_{max} 1,88 (1,38 – 4,52) h e menores valores de CL_R 4,08 (2,36 – 6,35) L/h e CL_{SEC} 3,95 (2,29 – 6,21) L/h de FUR. Ainda, após a primeira dose de CER, as pacientes gestantes apresentaram valores de C_{max}: 43,0 (32,1 – 51,7) µg/mL, T_{max}: 0,34 (0,29 – 0,46) h, AUC_{0-6}: 66,7 (45,1 – 77,4) µg×h/mL, $AUC_{0-\infty}$: 66,7 (45,1 – 77,4) µg×h/mL, $t_{1/2}$: 1,71 (1,32 – 1,82) h, CL_{ss}: 10,3 (8,65 – 15,6) L/h, Fe: 28,2 (13,2 – 43,6) %, CL_R: 3,01 (2,41 – 4,24) L/h, Vd_c: 24,2 (20,3 – 29,8) L, Vd_{ss}: 23,7 (19,4 – 26,6) L e Fu 0,67 (0,59 – 0,74). O tratamento com CER empregado mostrou-se efetivo para 9 pacientes para MIC = 2 µg/mL, para 5 pacientes para MIC = 4 µg/mL e para nenhuma paciente para MIC = 8 µg/mL. Já no segundo protocolo, as participantes gestantes saudáveis apresentaram menores valores de $AUC_{0-\infty}$ 1110,48 (1033,88 – 1362,50) ng×h/mL, Ae 7,75 (5,67 – 10,04) mg e Fe 19,39 (14,50 – 25,11) %, como também maiores valores de CL/F 38,17 (34,83 – 45,17) L/h e CL_{NR} 31,64 (27,91 – 41,16) L/h quando comparadas as participantes não gestantes saudáveis. Assim, conclui-se que a inflamação, avaliada pela pielonefrite aguda, reduziu a atividade *in vivo* dos OAT 1 e 3 em aproximadamente 50%. O estudo de PK-PD sugere que ajuste de dose de pelo menos 30% (dose total de aproximadamente 1 g) seria suficiente para que 8 das 10 pacientes investigadas apresentassem efetividade ($fT>_{MIC}$ ≥ 50%) para os MIC de 2 e 4 µg/mL. Finalmente, não se observou impacto da gestação na atividade *in vivo* dos OAT 1 e 3. No entanto, o aumento de aproximadamente 40% no CL_{NR} e de aproximadamente 50% no CL/F das gestantes sugere que outra via de eliminação e/ou de absorção pode estar alterada nesta condição.

Palavras-chave: Pielonefrite, Gravidez, Farmacocinética, Furosemida, OAT, Cefuroxima.

ABSTRACT

BENZI, J. R. L. **Impacts of pregnancy and acute pyelonephritis on *in vivo* activity of organic anion transporters 1 and 3 employing furosemide pharmacokinetics.** 2022. 181f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2022.

Organic anion transporters (OAT) 1 and 3 are of fundamental importance in renal excretion and consequently in the drug dosage regimen. However, little is known about the influence of inflammation associated with kidney infection, especially in pregnant women, on the expression/activity of these transporters. Thus, this study developed protocols to investigate inflammation and pregnancy in the *in vivo* activity of OAT 1 and 3 employing furosemide (FUR) pharmacokinetics. In the first protocol, the impact of inflammation was investigated in pregnant women diagnosed with acute pyelonephritis (inflammation model), in the second and third trimesters of pregnancy. Patients were treated with intravenous cefuroxime (CER) 750 mg TID and received a single oral dose of FUR 40 mg before (n = 10) and 40 mg after (n = 7) the end of antibiotic treatment, hospital discharge and reduction of inflammation. Plasma cytokine concentrations were evaluated in the two phases of this protocol. Additionally, we sought to describe the pharmacokinetics and PK-PD relation of CER against 3 possible MIC for *Escherichia coli* (2, 4 and 8 µg/mL) in this population. The second protocol of this study investigated the impact of pregnancy in 10 healthy pregnant participants and 12 healthy non-pregnant participants who received a single oral dose of FUR 40 mg. In all groups and phases, serial blood and urine samples were collected up to 24h after FUR administration. Methods for the quantification of FUR, FUR glucuronide and CER in biological matrices were developed and validated in LC-MS/MS. The kinetic disposition of the FUR was evaluated by the non-compartmental model. The impact of inflammation (before and after CER treatment) on FUR pharmacokinetics was assessed by the Wilcoxon test, while the impact of pregnancy (pregnant and non-pregnant) was assessed by the Mann-Whitney test. The significance level was set at 5% for both tests. The bioanalytical methods showed adequate sensitivity and confidence limits for pharmacokinetic studies, allowing the quantification of FUR, FUR glucuronide and CER within 24 h after the administered doses. When compared to the post-infection/inflammation period, pregnant women diagnosed with acute pyelonephritis had plasma cytokine concentrations from 2 to 100-fold higher for MCP-1, TNF-α, IFN-γ, IL-6 and up to 10-fold for the C-reactive protein. In addition, they had higher median values (interquartile range) of T_{max} 1.88 (1.38 - 4.52) h

and lower values of CL_R 4.08 (2.36 - 6.35) L/h and CLS_{EC} 3.95 (2.29 - 6.21) L/h of FUR. Also, after the first dose of CER, pregnant patients had C_{max} values: 43.0 (32.1 – 51.7) µg/mL, T_{max}: 0.34 (0.29 – 0.46) h, AUC_{0-6}: 66.7 (45.1 - 77.4) µg×h/mL, $AUC_{0-\infty}$: 66.7 (45.1 - 77.4) µg×h/mL, $t_{1/2}$: 1.71 (1.32 - 1.82) h, CL_{ss}: 10.3 (8.65 - 15.6) L/h, Fe: 28.2 (13.2 - 43.6) %, CL_R: 3.01 (2.41 - 4.24) L/h, Vd_c: 24.2 (20.3 - 29.8) L, Vd_{ss}: 23.7 (19.4 - 26.6) L and Fu 0.67 (0.59 - 0.74). The CER treatment used was effective for 9 patients for MIC = 2 µg/mL, for 5 patients for MIC = 4 µg/mL and for no patient for MIC = 8 µg/mL. In the second protocol, healthy pregnant participants had lower $AUC_{0-\infty}$ 1110.48 (1033.88 – 1362.50) ng×h/mL, Ae 7.75 (5.67 – 10.04) mg and Fe 19.39 (14.50 - 25.11) %, as well as higher values of CL/F 38.17 (34.83 - 45.17) L/h and CL_{NR} 31.64 (27.91 - 41.16) L/h when compared to healthy non-pregnant participants. Thus, we concluded that inflammation, assessed by acute pyelonephritis, reduced the *in vivo* activity of OAT 1 and 3 by approximately 50%. The PK-PD study suggests that a dose adjustment of at least 30% (total dose of approximately 1 g) would be sufficient for 8 of the 10 investigated patients to be effective ($fT_{>MIC} \geq 50\%$) for MIC of 2 and 4 µg/mL. Finally, there was no impact of pregnancy on the *in vivo* activity of OAT 1 and 3. However, the increase of approximately 40% in CL_{NR} and approximately 50% in CL/F in pregnant women suggests that another route of elimination and/or absorption may be altered in this condition.

Key-words: Inflammation. Pregnancy. Clinical Pharmacokinetics. Furosemide. OAT 1. OAT 3.

1. INTRODUÇÃO

A excreção renal é uma das principais formas de eliminação de fármacos, tendo o transporte ativo por transportadores uma importante contribuição nesta rota. Uma revisão da literatura mostra que a eliminação de 32% dos 200 fármacos mais prescritos nos Estados Unidos da América em 2010 se dá por excreção renal (> 25% da dose absorvida é eliminada de forma inalterada na urina). E destes, 92% são eliminados pelo menos em algum grau por secreção tubular (MORRISSEY et al., 2013). Os transportadores de ânions orgânicos (OAT) 1 e 3 compõem uma importante família de transportadores, contribuindo com a eliminação renal de anti-hipertensivos, diuréticos, estatinas, antivirais, antirretrovirais, antagonistas de receptores H2, anti-inflamatórios não esteroides, antibióticos e componentes endógenos. Apesar de suas relevantes contribuições, pouco se conhece sobre os fatores que modulam suas atividades ou expressão. O *International Transporter Consortium,* reconhecendo a importância dos OAT 1 e 3 na excreção renal de fármacos recomenda a investigação dos fatores que influenciam suas atividades e/ou expressão, como estados de doenças, interações fármaco-fármaco e populações especiais, como gestantes (CHU; CHAN e EVERS, 2017; EVERS et al., 2018; CHU et al., 2018; HUO e LIU, 2018; GIACOMINI; GALETIN e HUANG, 2018; ZAMEK-GLISZCZYNSKI, et al., 2022).

Sabe-se que a gravidez pode induzir alterações na farmacocinética. Os mecanismos destas mudanças mais bem caracterizados residem no aumento de fluxo sanguíneo do fígado e dos rins, aumento de volume plasmático e fração livre (Fu) dos fármacos (ANDERSON et al., 2005; CONSTANTINE, 2014; TASNIF; MORADO; HEBERT, 2016). Ademais, nas últimas décadas, tem se caracterizado a alteração de atividade das enzimas do citocromo P-450 (CYP) pelo emprego de fármacos marcadores (*probe drugs*). Por exemplo, o CYP3A4 é a isoforma mais importante no metabolismo de medicamentos e está induzido de 40-100% em todos os trimestres da gestação (ANDERSON et al., 2005; CONSTANTINE, 2014; TASNIF; MORADO; HEBERT, 2016), como observado em estudos clínicos com emprego dos fármacos marcadores midazolam e dextrometorfano (TRACY et al, 2005; HEBERT et al., 2008). Em contraste, ainda pouco se conhecesse sobre a atividade ou expressão dos transportadores de fármacos durante a gestação. Porém, é impossível estudar as alterações que a gravidez pode provocar na farmacocinética de todos os medicamentos. Logo, os estudos clínicos

passam a ser conduzidos com fármacos marcadores, caracterizando assim uma importante via da disposição cinética que pode ser extrapolada para outros medicamentos que a compartilhem.

Os fármacos marcadores de transportadores, como a furosemida empregada neste estudo, apresentam a desvantagem de serem pouco específicos, uma vez que podem também ser substratos de outros transportadores ou enzimas durante o processo de absorção, distribuição, metabolismo e eliminação. Porém, até o momento, seu uso representa um importante instrumento para investigações *in vivo* e *in vitro*, e recentes publicações recomendam seu uso (GIACOMINI e HUANG et al., 2022).

Adicionalmente, este trabalho buscou caracterizar o impacto da inflamação, empregando a pielonefrite como modelo, na atividade dos OAT 1 e 3 em gestantes. A inflamação é um processo de resposta do hospedeiro a estímulos nocivos físicos, químicos ou biológicos, caracterizado pelo aumento de fluxo sanguíneo, permeabilidade vascular e mediadores inflamatórios, como as citocinas (WRIGHT, 1997; CRESSMAN et al., 2012). As citocinas são proteínas solúveis envolvidos no recrutamento de leucócitos e ativação de outras linhagens celulares como fibroblastos, macrófagos, monócitos, linfócitos, neutrófilos e eosinófilos e são relacionadas aos sinais inflamatórios sistêmicos como febre, hipotensão e caquexia (CRESSMAN et al., 2012). Assim, durante o processo inflamatório, macrófagos ativados produzem e secretam citocinas pró-inflamatórias, tais como a interleucina (IL) 6, IL-1β, IL-8, fator de necrose tumoral (TNF) α e interferon γ (WRIGHT, 1997; CRESSMAN et al., 2012). Estudos em *in vitro*, em modelos experimentais e clínicos mostram que o aumento das concentrações plasmáticas de múltiplas citocinas pode alterar a expressão e/ou a atividade de transportadores de fármacos (WRIGHT, 1997; AITKEN et al., 2006; MORGAN et al., 2009; FARDEL e VÉE, 2009; CRESSMAN et al., 2012; COLOMBO e RODRIGUES, 2015; LANCHOTE et al., 2015; SEIFERT et al., 2017; EVERS et al., 2018; CARIS et al., 2020). Logo, a inflamação pode resultar em alterações nos parâmetros de absorção, distribuição, metabolismo e excreção dos fármacos, sendo considerada um importante fator na variabilidade da eficácia e toxicidade de medicamentos (LIPTROTT AND OWEN, 2011). Porém, investigações clínicas com emprego de fármacos marcadores são escassas, principalmente em populações como gestantes.

Assim, este estudo buscou caracterizar a atividade dos OAT 1 e 3 durante a gravidez e na presença de inflamação, pelo emprego do fármaco marcador furosemida. Os dados observados no presente estudo ampliam o entendimento da variabilidade intra

e interindividual na disposição cinética de medicamentos substratos dos OAT 1 e 3, e podem ser empregados para construção de regimes posológicos que maximizem a chance de eficácia terapêutica e redução da chance de ineficácia ou efeitos tóxicos.

Considerando o presente exposto, esta tese foi dividida em dois capítulos, os quais incluem os estudos clínicos e os métodos bioanalíticos. O **Capítulo I** apresenta a investigação do impacto da inflamação em pacientes gestantes diagnosticadas com pielonefrite aguda e da gestação, empregando a farmacocinética do fármaco marcador de atividade dos OAT 1 e 3, furosemida. O **Capítulo II** descreve o desenvolvimento e a validação dos métodos bioanalíticos de determinação da furosemida e glicuronídeo de furosemida em plasma, hidrolisado de plasma, ultrafiltrado de plasma e urina empregando os sistemas cromatografia líquida de alta eficiência acoplada à espectrometria de massas em tandem (HPLC-MS/MS). Adicionalmente, este capítulo descreve o desenvolvimento e validação de método bioanalítico de determinação da cefuroxima em plasma, ultrafiltrado de plasma e urina por cromatografia líquida de ultra eficiência acoplada a espectrometria de massas em tandem (UPLC-MS/MS). Como a cefuroxima foi utilizada no tratamento da pielonefrite aguda, este capítulo também descreve o estudo de farmacocinética-farmacodinâmica da cefuroxima nesta população.

CONCLUSÕES

1. Os métodos de determinação de furosemida e seu metabólito glicuronídeo de furosemida em matrizes biológicas empregando HPLC-MS/MS apresentaram sensibilidade e limites de confiança adequados para estudos de farmacocinética, possibilitando a quantificação de furosemida e glicuronídeo de furosemida em até 24 h após a administração de dose oral única de 40 mg.

2. As gestantes diagnosticadas com pielonefrite aguda apresentaram concentrações de citocinas plasmáticas de 2 até 100 vezes maiores para a MCP-1, TNF-α, IFN-γ, e IL-6, bem como de até 10 vezes para a proteína C reativa, quando comparadas ao período pós-infecção/inflamação.

3. A pielonefrite aguda em gestantes reduziu a atividade *in vivo* dos OAT 1 e 3 em aproximadamente 50%, avaliada pelo emprego da furosemida como fármaco marcador.

4. O CL_M do glicuronídeo de furosemida apresentou diferença marginal ($p = 0,07$) entre a primeira fase (antes do tratamento) e a segunda fase (após o término do tratamento com cefuroxima) na população de gestantes diagnosticadas com pielonefrite aguda.

5. Não se observou impacto da gestação na atividade *in vivo* dos OAT 1 e 3, avaliada pelo emprego da furosemida como fármaco marcador. No entanto, o aumento de aproximadamente 40% no CL_{NR} e de aproximadamente 50% no CL/F sugere que outra via de eliminação e/ou de absorção pode estar alterada nesta condição.

6. Os métodos de determinação das concentrações plasmáticas de cefuroxima total e cefuroxima livre, assim como de cefuroxima na urina, se mostraram sensíveis, seletivos e com parâmetros de validação aceitáveis para estudos de farmacocinética e PK-PD.

7. Os parâmetros farmacocinéticos da cefuroxima nas gestantes diagnosticadas com pielonefrite aguda são comparáveis aos reportados para não gestantes, sendo que o CL_R representa aproximadamente metade do CL.

8. O estudo de PK-PD da cefuroxima sugere que o ajuste de dose de pelo menos 30% (dose total de aproximadamente 1 g) seria suficiente para que 8 das 10 pacientes investigadas apresentassem efetividade ($fT>_{MIC} \geq 50\%$) para os MIC de 2 e 4 μg/mL.

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