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Avaliação de reações adversas a medicamentos utilizados em pacientes com doenças crônicas no Hospital Universitário Regional de Maringá

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde do Centro de Ciências da Saúde da Universidade Estadual de Maringá, como requisito parcial para obtenção do título de Doutor em Ciências da Saúde.
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Knowing is not enough; we must apply. Willing is not enough; we must do.

(Goethe)

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SUMÁRIO

RESUMO GERAL

Medicamentos são, em geral, seguros e efetivos, mas as reações adversas podem ocorrer e serem fatais (WESTER, et al., 2008). A resposta aos medicamentos varia muito entre os indivíduos, de acordo com a constituição genética, idade, sexo, co-morbidades, incluindo fatores ambientais como dieta e estilo de vida (tabagismo e consumo de álcool, por exemplo), e a presença de outros medicamentos (SIROT et al., 2006). Pacientes normalmente recebem vários medicamentos ao mesmo tempo, seja devido a doenças que necessitam de terapias combinadas, ou porque apresentam comorbidades, cada uma das quais sendo tratada com um ou mais agentes. Nestes casos existe grande possibilidade que uma interação entre drogas ocorra, podendo uma alterar a farmacodinâmica ou farmacocinética da outra. Na maioria das vezes, a interação não apresenta significado clinico. Somente quando a magnitude da alteração produzida no organismo humano é grande o suficiente é que a interação se torna clinicamente significativa, causando uma reação adversa. Segundo a Organização Mundial de Saúde (OMS), Reação Adversa a Medicamento (RAM) é definida como: "qualquer resposta a um fármaco que seja prejudicial, não intencional, e que ocorra nas doses normalmente utilizadas em seres humanos para profilaxia, diagnóstico e tratamento de doenças, ou para a modificação de uma função fisiológica" (WHO 2002). Segundo Lazarou e cols. (1998) reação adversa a medicamentos aparece entre a quarta e a sexta causa mais comuns de morte nos Estados Unidos. No Reino Unido, um estudo observacional prospectivo, demonstrou que RAMs representaram cerca de 6% do total de admissões ao sistema de saúde por ano (PIRMOHAMED et al., 2004). RAMs também ocorrem dentro do hospital e aproximadamente 15% dos pacientes hospitalizados desenvolvem uma RAM; sendo que em 25% dos casos isto leva a um prolongamento de permanência hospitalar sendo um indicador, de acordo com a OMS, da gravidade da RAM (DAVIES et al. 2009). Há vários fatores predisponentes para a ocorrência de RAMs. Uma área importante a considerar é o papel das interações medicamentosas (IMs). Interação medicamentosa é definida como uma alteração clinicamente significativa no efeito de uma droga (droga objeto), como resultado da administração conjunta de outro (fármaco precipitante) (PIRMOHAMED et al., 2004). Podem ser classificadas como interação farmacocinética (a disponibilização da droga objeto em seu local de ação é alterada pelo medicamento precipitante) ou farmacodinâmica (resposta da droga objeto é modificada pelo precipitante sem alterações na farmacocinética da droga objeto). Um estudo retrospectivo, com 520 pacientes, realizado em diferentes

clínicas em um hospital demonstrou que interações potenciais foram observadas em 51% dos pacientes na admissão e em 63% dos pacientes na alta hospitalar (FOKTER et al., 2010). No Brasil, um estudo de caso-controle retrospectivo revelou que a prevalência de IMs potenciais foi positivamente associada com o sexo e idade do paciente. A maior taxa de IMs ocorreu em mulheres com idade maior que 55 anos (CRUCIOL-SOUZA ; THOMSON, 2006). Ao visualizarmos o futuro e os avanços da medicina é provável que terapias com múltiplas drogas sejam obrigatórias para o tratamento de certas doenças. Na verdade, já está acontecendo; tomemos o exemplo de infarto agudo do miocárdio. Entre 1990 e 2001, a proporção de sobreviventes que tomaram mais de três medicamentos cardíacos aumentou de 13% para 74% (SPENCER et al. 2005; FLOYD, 2009) . Com relação a classificação de RAM, existem inúmeras, sendo a mais aceita é a de Rawlins e Thompson (1991), que as classifica em reações do tipo A ou previsíveis, e as reações do tipo B ou imprevisíveis. As reações do tipo A representam um aumento das ações farmacológicas de uma droga. São dependentes da dose e são, portanto, facilmente reversíveis com a redução da dose ou a suspensão da droga. Em contraste, as reações adversas do tipo B são bizarras e não podem ser previstas a partir da farmacologia da droga. Muitas reações do tipo B podem ser imunologicamente mediadas (PIRMOHAMED et al., 1998). Interações medicamentosas são exemplos da primeira e anafilaxia da segunda. A descoberta da associação entre hipersensibilidade a fármacos e alelos HLA específicos foi um grande avanço e tem possibilitado que as reações de hipersensibilidade do tipo B possam ser previsíveis e evitáveis (ALFIREVIC; PIRMOHAMED, 2010). Assim, o objetivo desta pesquisa foi identificar e avaliar reações adversas a medicamentos utilizados para tratamento de pacientes portadores de doenças crônicas no Hospital Universitário Regional de Maringá (HUM). Para realização do estudo, informações foram resgatadas das notificações voluntárias submetidas á Divisão de farmacovigilância do HUM. Estas notificações dos casos suspeitos de RAM em pacientes atendidos no HUM são realizadas por médicos e farmacêuticos. Esta tese de doutoramento em Ciências da Saúde está apresentada na forma de dois artigos científicos. No primeiro artigo, redigido sob a forma de relato de caso, foi demonstrado um significativo aumento do tempo de protrombina (PT) e da Relação Normalizada Internacional do tempo de protrombina (RNI), em paciente de 62 anos, com prótese valvular mecânica em posição mitral, estabilizada anteriormente com anticoagulante cumarínico após introdução de Levotiroxina na terapia do paciente. O RNI do paciente estava dentro da faixa terapêutica (2,5-3,5) no mês anterior quando em uso de femprocumona (3mg /d), mas tornou-se supraterapêutico após o início de tratamento por 30

dias com levotiroxina com sangramento importante e RNI não registrável (> 9). Este caso permite sugerir que seria aconselhável na prática clínica, monitorar as alterações do tempo de protrombina ao incluir ou excluir levotiroxina ou qualquer droga suspeita de causar uma interação para pacientes em terapia com anticoagulantes cumarínicos. Este trabalho será submetido ao periódico **Journal of Clinical Pharmacy and Therapeutics** (ISSN. 1365-2710). No segundo artigo são relatados dois casos de síndrome de hipersensibilidade a anticonvulsivante induzida por drogas antiepilépticas com anel aromático, como a Carbamazepina e Fenitoína, e a associação com alelos do antígeno leucocitário humano (HLA), em crianças brasileiras do sexo masculino. Esta reação também denominada Reação à droga com eosinofilia e sintomas sistêmicos, para a qual a denominação mais apropriada seria DRESS, decorrente da expressão em inglês "Drug Rash with Eosinophilia and Systemic Symptons" (BOCQUET et al., 1996; SCHLIENGER; SHEAR, 1998; FLEMING; MARIK, 2011). Esta síndrome é caracterizada por erupção cutânea extensa mucocutânea, febre, linfadenopatia, hepatite, anormalidades hematológicas com eosinofilia e linfócitos atípicos, e pode envolver outros órgãos com infiltração eosinofílica, produzindo danos a vários sistemas, especialmente os rins, coração, pulmões e pâncreas. Reações de hipersensibilidade induzidas por drogas representam um grupo heterogêneo de RAM tipo B que se manifestam com uma grande variedade de sintomas e sinais clínicos, e pode ser iniciada por uma vasta gama de compostos químicos estruturalmente diversos (ALFIREVIC; PIRMOHAMED, 2010). Esta síndrome, como dito anteriormente foi descrita pela primeira vez para anticonvulsivantes com anel aromático como a carbamazepina, fenitoína e fenobarbital (BOCQUET et al., 1996; SCHLIENGER;SHEAR, 1998). O diagnóstico de DRESS foi estabelecido com base em critérios de diagnóstico RegiSCAR-DRESS (KARDAUN et al., 2007) em ambos os casos. Após a interrupção dos anticonvulsivantes, os pacientes apresentaram melhora dos sintomas clínicos e dos resultados de laboratório. Nenhuma outra condição médica foi identificada para explicar este evento e, além dos anticonvulsivantes, os pacientes não usaram outras drogas. Os anticonvulsivantes com anel aromático são metabolizados em compostos aromáticos hidroxilados tais como os óxidos de areno. Se a biotransformação deste metabólito tóxico é insuficiente, o metabólito pode ligar-se a macromoléculas celulares causando necrose celular ou uma resposta imunológica secundária. Reatividade cruzada entre os anticonvulsivantes aromáticos pode ocorrer em 75% dos casos. Além disso, há uma tendência familial de hipersensibilidade a anticonvulsivantes (KNOWLES et al., 1999). As reações cutâneas graves adversas, tais como síndrome de Stevens-Johnson/necrólise

epidérmica tóxica e a DRESS têm sido associadas, durante a última década, com alelos Classe I e II do HLA, impulsionando o conhecimento de sua imunopatogenia (LONJOU et al., 2006; PAVLOS et al., 2012). A descoberta dessas associações criou a promessa de que os riscos para essas reações podem ser previstos por meio de triagem de farmacogenética, evitando morbidade e mortalidade associada a este tipo de reações. De conhecimento dos autores este é o primeiro relato de caso que descreve DRESS induzida por fármacos antiepilépticos com anel aromático em crianças brasileiras onde foram identificados alelos HLA classe I e II. Este trabalho foi submetido ao periódico **International Journal of Clinical Pharmacy** (IJCP) (ISSN 2210-7703). Nosso estudo propõe que relato de caso seja a pedra angular da farmacovigilância, fornecendo as primeiras evidências das possíveis reações adversas durante a utilização clínica dos medicamentos comercializados. Apesar da eficácia demonstrada, em ensaios clínicos, dos agentes farmacológicos atualmente prescritos, resultados ótimos não são sempre observados, existindo a possibilidade de interações medicamentosas e eventos adversos graves, não detectados anteriormente. A descoberta do perfil de reações adversas a um medicamento antes da comercialização (estudo pré-clínico) está inteiramente dentro da esfera da indústria farmacêutica e, portanto, têm a responsabilidade em fornecer informação adequada sobre um novo produto. Após a comercialização, a responsabilidade por expandir o conhecimento das reações adversas de uma nova droga se difunde para todos, assim quando os medicamentos são usados por profissionais da saúde informados e por pacientes que entendem e compartilham a responsabilidade por seus medicamentos, o risco de danos é menor. Usando métodos e ferramentas farmacogenomicas, esperamos reconhecer os fármacos com maior risco para essas complicações e cumprir a promessa de uma medicina personalizada para o tratamento de pacientes com doenças graves.

Palavras-chave: reações adversas a medicamentos, interações medicamentosas, levotiroxina, femprocumona, anticonvulsivantes, Síndrome DRESS, antígenos HLA.

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Artigo 1: Interaction Between Levothyroxine and Phenprocoumon – A Case Report

Interaction between Levothyroxine and Phenprocoumon: A Case Report

Abbreviated title: Anticoagulants drug interaction

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Keywords: drug-drug interaction, levothyroxine, overanticoagulation, phenprocoumon

SUMMARY

What is known and Objective: Several case reports have associated the combined use of thyroid drugs and oral anticoagulants, like coumarin, with overanticoagulation. However, this effect has never been described for phenprocoumon, a coumarin derivate that is widely prescribed in continental European countries and in Latin America. *Case summary:* We describe a 62-year-old female who had an unexpectedly labile anticoagulation profile when levothyroxine (Puran T4®) was added to her drug therapy regimen, which included phenprocoumon (Marcoumar®). This resulted in an elevated international normalized ratio (INR) that was unrecordable and bleeding (macroscopic hematuria) that required hospitalization and treatment with vitamin K. The patient had been taking phenprocoumon for almost ten years for systemic embolism prophylaxis because of her history of mechanical bileaflet mitral valve prosthesis. One month before the events described, the patient was prescribed sodium levothyroxine (50 mcg daily) to treat hypothyroidism (TSH = 40 μU/mL; reference range, 0.40–4.0 μU/mL). Approximately 3 weeks prior to initiation of levothyroxine treatment, her INR was 2.8. A drug interaction was therefore suspected. The Horn Drug Interaction Probability Scale (DIPS) indicated a probable interaction between oral phenprocoumon and levothyroxine in this case. *What is new and conclusion:* Clinicians should be aware that levothyroxine may interact with oral phenprocoumon, resulting in overanticoagulation. If levothyroxine is introduced into a drug therapy regimen that contains phenprocoumon, the patient INR should be monitored to guide adjustment of phenprocoumon and levothyroxine dosages.

WHAT IS KNOWN AND OBJECTIVE

Phenprocoumon is a coumarin-type oral anticoagulant (OAC), or vitamin K antagonist (VKA), which is widely prescribed in continental European and Latin American countries for the prophylaxis and treatment of thromboembolic events. The most common complication of this OAC is bleeding, with major bleeding events occurring in 1–3% of patients annually. Because of the narrow therapeutic range of this drug, many patients experience bleeding of variable severity or recurrent thrombotic events.[1-5] Monitoring of international normalized ratio (INR) and dose adjustments are frequently required during OAC therapy and are influenced by changes in concomitant medications, diet, alcohol consumption, acute illness, liver disease, and unknown factors.[6]

Phenprocoumon is rapidly absorbed after oral administration, is highly protein-bound to albumin (99%), and is eliminated almost exclusively through hepatic metabolism via the cytochrome P450 system (CYP). Compared to warfarin and acenocoumarol, phenprocoumon metabolism is less dependent on the polymorphic CYP2C9 enzyme, but may be more liable to CYP3A4-mediated drug interactions.[7,8] Phenprocoumon consists of 2 isomers: R and S. S-phenprocoumon is 1.5–2.5 times more potent than R-phenoprocoumon and the half-life of racemic phenprocoumon is 156–172 h.[2]

OACs are frequently used concomitantly with thyroid hormones like levothyroxine.[9] Some medical textbooks[10,11] and electronic databases[12] point out the potential for an interaction between thyroid hormones and coumarin anticoagulants, resulting in overanticoagulation. However, this effect has never been described for phenprocoumon. Because phenprocoumon metabolism differs somewhat from that of other OACs, it is important to investigate the occurrence of drug interactions between phenprocoumon and levothyroxine.

In this case report, we describe an adult woman who had an unexpectedly labile anticoagulation profile when levothyroxine was added to her drug therapy regimen, which included phenprocoumon.

DETAILS OF THE CASE

A 62-year-old woman was admitted to the hospital because of macroscopic hematuria during 5 days after and an unrecordable INR. She denied chest pain and shortness of breath. Ten years ago, she had received a mechanical bileaflet mitral valve prosthesis because of severe mitral valve insufficiency. The patient had a history of atrial fibrillation and chronic heart failure. She was receiving long-term phenprocoumon (Marcoumar®) therapy and was maintaining a stable INR within the therapeutic range (target INR: 2.5–3.5). Fifteen days before starting levothyroxine (Puran T4®; 50 mcg daily) treatment for hypothyroidism, her INR was 2.8. Twenty-six days after starting oral levothyroxine, the patient's INR rose to an unrecordable value and she began experiencing macroscopic hematuria. She was admitted to the hospital 5 days after the onset of macroscopic hematuria. On admission, there were no symptoms of any intercurrent illness and laboratory results, including liver function tests, were normal. A chest X-ray radiograph showed borderline cardiomegaly. Medications taken by the patient as part of a chronic therapy regimen were as follows: phenprocoumon (3 mg/day), which the patient stopped taking after the onset of macroscopic hematuria and resumed on the day of admission; carvedilol (6.25 mg/day); captopril (50 mg/day); furosemide (40 mg/day) spironolactone (25 mg/day); levothyroxine (50 mcg/day); and digoxin (0.125 mg/day). A thorough history did not identify any change in diet, concomitant medication, food supplements, or drug therapy compliance. On the day of admission, the concomitant medication regimen remained unchanged, but phenprocoumon was discontinued immediately and she was given

vitamin K (10 mg, intravenously) and fresh frozen plasma. Twenty-four hours later, her INR decreased to 2.14 (Figure 1). Hemoglobin concentration was considered satisfactory and the hematuria spontaneously resolved several hours after admission. Anticoagulation with phenprocoumon was resumed 5 days after the hematuria resolved, but at a lower dose of 1.5 mg daily. The patient's INR rose 3 days after resuming phenprocoumon therapy to 6.79. This INR increase was smaller than that observed with higher doses of phenprocoumon. Phenprocoumon was stopped on the 8th day of hospitalization and levothyroxine was stopped on the 10th day of hospitalization. The patient was discharged 17 days after hospital admission. At discharge, the patient had an INR of 5.0 and a TSH value of 12 (reference range: 0.40–4.0 μU/mL). The patient was taking the same medications at the time of discharge as at the time of admission, with the exception of phenprocoumon and levothyroxine.

DISCUSSION

In this case report we show a clinically significant increase in the INR of an adult female patient who had been stable with phenprocoumon therapy until levothyroxine was introduced into her treatment regimen. The INR rose when phenprocoumon was used concomitantly with levothyroxine, but lowered when this association was discontinued. No specific medical conditions were identified to explain this event, and apart from levothyroxine, none of the prescribed drugs were suspected to affect the anticoagulant effect of phenprocoumon. According to the Horn Drug Interaction Probability Scale (DIPS),[13] there is a probable interaction between oral phenprocoumon and levothyroxine. This is the first case report describing an interaction between phenprocoumon and levothyroxine.

Coumarin derivatives act as competitive inhibitors of vitamin K epoxide reductase (VKORC1), which is responsible for regenerating reduced vitamin K from vitamin K epoxide after it has been consumed as a co-factor in the synthesis of coagulation factors II, VII, IX, and X.[6] While all OAC have a similar mechanism of action and a similar chemical structure, there are substantial differences in their clinical pharmacokinetics.[8] Therefore, while pharmacodynamic interactions may occur with all drugs of this group, the pharmacokinetics of the interactions should be observed separately for each drug.

An extensive review of clinical databases was performed to further investigate the potential mechanism of this interaction. The hypoprothrombinemic response to acenocoumarol and warfarin may be enhanced when thyroid hormone supplementation is added to patient drug therapy regimens. However, no significant effects are expected when acenocoumarol or warfarin is added to patients who are stable under thyroid replacement therapy.[12] The exact mechanism of the interaction among levothyroxine and OAC has not been established. Mechanisms of such interactions may include both pharmacokinetic and pharmacodynamic mechanisms, and may result in either hyper- or hypoprothrombinemia.[14]

More than 40 years ago, sodium dextrothyroxine was reported to augment the anticoagulant effect of warfarin by increasing the rate of metabolism of coagulation factors.[15] A recent experimental study indicated that thyroxine treatment increased plasminogen activator activity in the kidney.[16] The plasma levels of vitamin K-dependent coagulation factors FII, FVII, FIX, and FX are significantly reduced under the influence of hormones in the hypothalamic-pituitary-thyroid axis.[17]. Because pharmacodynamic interactions may occur with all OAC, the available literature suggests that a possible mechanism for the interaction between phenprocoumon and levothyroxine that results in an increased anticoagulant effect is a levothyroxine-induced increase in the rate of coagulation

factor metabolism, as described for the interaction between acenocoumarol and thyroid hormones[18] and between warfarin and dextrothyroxine.[15] However, further validation is required.

The pharmacokinetic mechanism of this interaction is not clear. An increased absorption of phenprocoumon is an unlikely mechanism, because phenprocoumon is almost completely absorbed when administered alone. An interaction between these drugs due to protein displacement of phenprocoumon (plasma protein binding 98-99%) by levothyroxine (plasma protein binding 99%) is likely because of the high rate of protein binding for levothyroxine.[19] However, the delayed onset of the clinical result raises some doubt about this mechanism. A change in the apparent volume of distribution is also unlikely because the patient was not edematous at any time and had normal serum creatinine. An interaction due to interference in the metabolism of phenprocoumon is not likely, as phenprocoumon is metabolized by CYP3A4 and CYP2C9, while levothyroxine is metabolized by deiodination.

In the case described here, the onset of overanticoagulation occurred 26 days after initiating the concomitant use of phenprocoumon and levothyroxine. This period of delay is similar to the delay that has been reported in other studies for the onset of adverse prothrombin time response (1 day–3 weeks) after the addition of other drugs to the pharmacotherapy regimen of patients taking phenprocoumon.[20] This delay may result from the long half-life of levothyroxine, as the peak therapeutic effect at a given dose of levothyroxine sodium may not be obtained for 4–6 weeks.[19]

WHAT IS NEW AND CONCLUSION

In this case report, an overanticoagulation effect due to a probable interaction between phenprocoumon and levothyroxine was described. Clinicians should be made aware of this potential interaction and adjust doses of phenprocoumon as necessary when initiating or discontinuing levothyroxine therapy. The complex response of coumarins to concomitant drug therapy makes it difficult to predict whether, and to what degree, anticoagulant control might deteriorate in individual patients. If levothyroxine is introduced into a drug therapy regimen that contains phenprocoumon, the patient INR should be monitored to guide adjustment of phenprocoumon and levothyroxine dosages. Patients exposed to this potential drug interaction should be advised when to seek medical attention, should symptoms of overanticoagulation occur.

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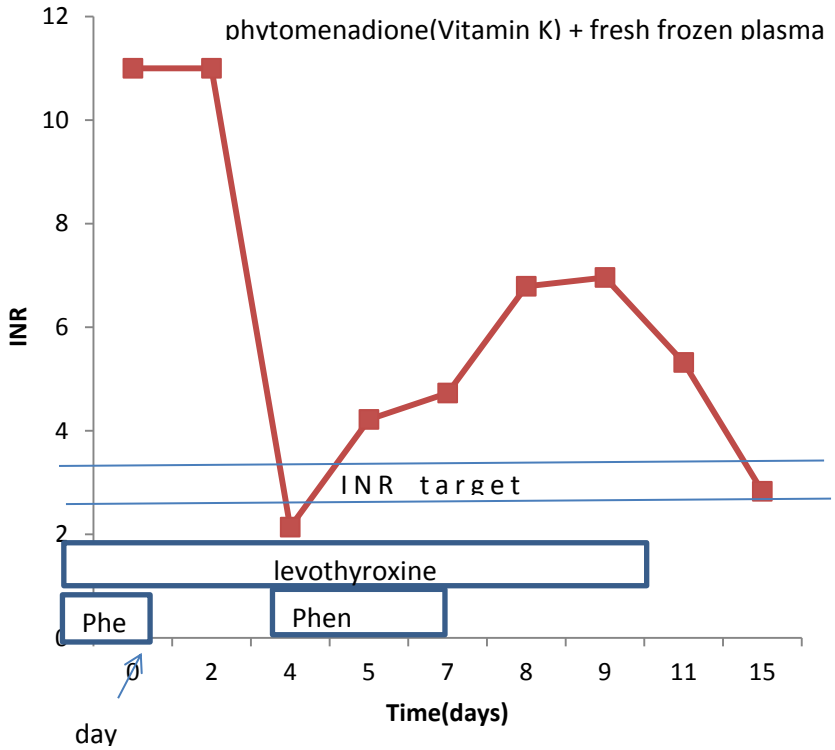

Figure 1. International normalized ratio (INR) measurements from time of admission until hospital discharge for a 62-year-old female patient experiencing a suspected interaction between phenprocoumon and levothyroxine. Boxes indicate days on which the respective drugs were administered.

Artigo 2: HLA typing in Brazilian boys with aromatic antiepileptic drug-induced DRESS

HLA typing in Brazilian boys with aromatic antiepileptic drug-induced DRESS

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Keywords: Anticonvulsant drugs, adverse drug reactions, DRESS syndrome, HLA Antigens

Abbreviated title: DRESS syndrome and HLA-B allele

ABSTRACT

In this work we report two cases of DRESS syndrome associated with the use of carbamazepine and phenytoin in white Brazilian boys who were tested for HLA-class I and II alleles. The clinical manifestations were similar: a maculopapular eruption progressing to exfoliative erythroderma, fever, and lymphadenopathy. Leukocytosis, atypical lymphocytes and liver injury were also observed. Assessment of causality using the Naranjo algorithm established in these cases a “possible” (score 6) relationship. Human leukocyte class I antigen (HLA Class I) genes have been identified as predictors for certain severe cutaneous adverse drug reaction syndromes, although HLA alleles and drug hypersensitivity is drug, disease phenotype, and ethnicity specific. Nonetheless, none of the reported cases presented either HLA-B-0801-TNF2-DRB1*03-DQB1*02 or HLA-A*3101.

HLA typing in Brazilian boys with aromatic antiepileptic drug-induced DRESS

Introduction

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is a life-threatening adverse drug reaction characterized by extensive mucocutaneous rash, fever, lymphadenopathy, hepatitis, hematological abnormalities with eosinophilia, and atypical lymphocytes. In addition, it can involve other organs via eosinophilic infiltration, and damage systems such as the kidneys, heart, lungs, and pancreas [1]. This syndrome was first described as a reaction to the aromatic antiepileptic drugs (AEDs) carbamazepine (CBZ), phenytoin (PHY), and phenobarbital; therefore, it was referred to as anticonvulsant hypersensitivity syndrome (AHS) [1].

At present, we have only a poor understanding of the mechanisms that cause this potentially life-threatening syndrome. Defective detoxification of reactive oxidative metabolites, altered immune response, sequential reactivation of herpes virus, and association with human leukocyte antigen (HLA) alleles have all been implicated in the pathophysiology of DRESS [1]. Recent studies have reported strong associations between certain HLA alleles and susceptibility to drug hypersensitivity [1]. However, to the best of our knowledge, most of these studies were performed with adult Asian or European patients, while data from children with multi-ethnic backgrounds is scarce [2].

DRESS is of great concern in the pediatric population, given the widespread use of AEDs. Here, we report 2 cases of DRESS induced by aromatic AEDs in Brazilian boys from the northwest of Parana's State tested for HLA class I and II alleles, and review the related literature.

Insert table 1 here.

Case 1

A 9 year-old Brazilian boy with white skin color (weight: 36 kg; height: 1.32 m), was admitted to the emergency department (ED) of a Brazilian university-based teaching hospital. He presented with fever (body temperature: 39°C), and a widespread erythematous pruritic maculopapular confluent eruption over the face, trunk and upper limbs (Figure1), with edema of the face and both hands. Symptoms were noted 27 days after initiating CBZ therapy (orally; 200 mg daily) for an idiopathic seizure disorder diagnosed 1 month prior to admission. The patient had not received CBZ treatment or therapy involving any other aromatic AED previously, and was not using any other drug concomitantly (with or without medical prescription) upon hospital admission. On physical examination, palpable lymphadenopathy in the cervical and inguinal regions was noted. In addition, the liver was palpable 2 cm below the right costal margin with fibroelastic consistency. The oropharynx and oral mucosa showed mild hyperemia. Hematologic and blood chemical tests revealed eosinophilia, leukocytosis, and elevated liver enzyme levels (Table 1). Serological test results for viral hepatitis (types A, B, and C), mumps, parvovirus B19, and human immunodeficiency virus were negative. Cytomegalovirus (CMV), immunoglobulin (IgG and IgM) serum antibodies, and Epstein-Barr virus capsid antigen-specific IgM and IgG antibodies did not indicate primary infection or reactivation. Skin biopsy showed dermatitis characterized by lymphocytic infiltrate of perivascular distribution without viral inclusions.

Given the association of fever, enlarged lymph nodes, marked leukocytosis with eosinophilia and atypical lymphocytosis, skin rash characteristics, and liver involvement, a diagnosis of DRESS was established based on RegiSCAR diagnostic criteria [1]. CBZ therapy was discontinued immediately after a total of 30 days and the following therapeutic

regimen was prescribed: dexchlorpheniramine (orally; 2 mg, 3 times a day) for 13 days and methylprednisolone (intravenous [IV]; 10 mg/kg/dose) for 8 days. The rash soon improved, but edema of the face persisted. Prednisolone (orally; 1–2 mg/kg/day) was administered for 11 days. Vancomycin (IV; 40 mg/kg/day) was administered for 7 days to treat a *Staphylococcus aureus* infection identified on blood culture examination, which was performed after the patient presented with fever. The patient's clinical symptoms and test results improved (Table 1) immediately after corticotherapy with oral prednisolone, and he was discharged 21 days after admission. Assessment of causality using the Naranjo algorithm indicated a "probable" relationship (score 6) between the adverse drug reaction and the use of CBZ. The patient presented the following results of HLA typing: HLA-A*02,29 B*44,50 C*06,16 DRB1*01,07 DQA1*01,02. The result for DQB1* allele was inconclusive in this case.

Case 2

An 11-year-old Brazilian boy with white skin color (weight: 41 kg; height: 1.59 m) was admitted to a Brazilian university-based teaching hospital with fever (body temperature: 39.4°C), generalized pruritic maculopapular rash associated with cough, and abdominal distension for the last 7 days. Fifteen days prior to admission, he was administered PHY therapy (orally; 100 mg, 2 times a day) for an idiopathic seizure disorder. The patient had not received PHY treatment or therapy involving any other aromatic AED previously, and was not using any other drug concomitantly (with or without medical prescription) upon hospital admission. On physical examination, he had enlarged axillary and inguinal lymph nodes, widespread erythematous pruritic maculopapular confluent eruption, edema of the face, and purpuric lesions on the extremities. The oropharynx and oral mucosa indicated mild hyperemia. Hematologic and blood chemical

tests revealed leukopenia with eosinophilia and slightly elevated aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GammaGT) levels (Table 1). Hepatomegaly was not observed.

Given the association of fever, enlarged lymph nodes, leukopenia with eosinophilia and skin rash characteristics, a diagnosis of DRESS was established based on RegiSCAR diagnostic criteria [1]. PHY therapy was discontinued on the 2nd day of hospitalization, and the patient was administered acetaminophen (orally; 400 mg, every 6 hours) and dexchlorpheniramine (orally; 2 mg, 3 times a day) for 3 days. Significant improvement in his condition was noted, and the erythematous rashes faded. On the 5th day of hospitalization, the patient's clinical condition worsened, with intense pruritus, confluent erythema of the back, desquamation, increasing facial edema, elevated liver enzyme levels, and hemodynamic instability. Dipyrone (orally; 500 mg, every 6 hours) was prescribed due to fever episodes (body temperature: 39°C). Results for anti-CMV (IgM) microparticle enzyme immunoassay (MEIA) were found to be positive 3 weeks after the onset of rash. Corticosteroid therapy (methylprednisolone IV; 40 mg every 6 hours for 5 days) was initiated at this time along with acyclovir (orally; 200 mg, every 4 hours for 5 days). On the 10th day of hospitalization, a skin biopsy specimen showed features of subacute dermatitis in the form of parakeratosis, irregular acanthosis, spongiosis, and superficial dermal edema, along with intense perivascular and periadnexal lymphomononuclear infiltrate in the dermis. On the 18th day of the patient's hospital course (16 days after withdrawal of the suspicious drugs), complications such as oliguria, abdominal pain, generalized edema, and arterial hypertension were noted. Therapy with furosemide (IV; 20 mg, twice a day for 2 days) and hydrocortisone (IV; 10 mg/kg/day, for 12 days) was initiated. The steroid treatments were soon changed to prednisolone (orally; 1–2 mg/kg/day) on alternate days for 6 days. After a few days, the skin eruption healed with desquamation. The patient was

discharged 30 days after admission with improved clinical symptoms and laboratory findings (Table 1). Assessment of causality using the Naranjo algorithm identified a "probable" relationship (score 6) between the adverse drug reaction and the use of PHY. HLA typing of this patient revealed the following: HLA-A*23,24 B*39,53 C*04,07 DRB1*04,08 DQA1*03,05 DQB1*03,03.

Discussion

Here, we report 2 cases of DRESS induced by aromatic AEDs (CBZ and PHY) in Brazilian boys who tested negative for the HLA-B*1502 allele. After discontinuation of the aromatic AEDs, the patients exhibited improvement in clinical symptoms and laboratory results. No specific medical conditions were identified to explain this event, and apart from aromatic AEDs, the patients did not receive any other medication. To the best of our knowledge, this is the first case report to describe DRESS induced by aromatic AEDs in Brazilian boys, and to describe a potential association of this event with HLA alleles.

The patients in this study were classified as brazilian whites according to skin color. They were born in the north-northwest of the state of Paraná and the inhabitants living in this region, including White people, present a variable, but considerable mixture of African (12.5%) and Amerindian contribution (7%) as evaluated by HLA polymorphism (Probst, Bompeixe, Pereira et al., 2000).

Numerous studies have reported reactivation of HHV-6 in the development of this syndrome [3-5]. Furthermore, it has also been suggested that reactivation of other herpes viruses, such as cytomegalovirus (CMV), may also be involved. Although the patient in Case 2 presented IgM anti-CMV antibodies—a sensitive and specific indicator of an ongoing or recent CMV infection—the patient in Case 1 did not show any evidence of

reactivation. It has been proposed that in susceptible people, a transient drug-induced hypogammaglobulinemia creates an immunological environment that permits viral reactivation. However, it is still a matter of debate whether reactivation of herpesviruses is part of the syndrome or whether it should be interpreted as a complication, resulting in a more protracted and relapsing disease course [1]. In addition, there is a familial tendency to anticonvulsant hypersensitivity, and with regard to the immunologic cross-reactivity among aromatic anticonvulsants, the data are contradictory [1].

The pathogenesis of drug hypersensitivity reactions seems to be mediated by the immune system, and it is increasingly apparent that individuals can be genetically predisposed to adverse drug reactions [6]. In particular, HLA Class I genes have been identified as predictors for certain severe cutaneous adverse drug reaction syndromes, although HLA and drug hypersensitivity is reportedly drug-, disease phenotype-, and ethnicity-specific [7]. One possibility is that antigenic peptides modified by small therapeutic drugs or their metabolites during endogenous antigenic processing may be presented by HLA class I antigens to CD8-specific cytotoxic T cells. This would then cause effector cytotoxic responses. Alternatively, the drug or its metabolites could interact with HLA antigens directly at the cell surface and alter a self-HLA peptide complex, which would then be recognized by CD8+ T cells [8]. Studies have found that HLA-B*1502 is associated with PHY- and CBZ-induced Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in some Asian populations [7,9]. Because of the strong association between HLA-B*1502 and PHY or fosphenytoin-induced SJS/TEN, healthcare providers should consider avoiding using these drugs as alternatives for carbamazepine in patients who test positive for HLA-B*1502 (data concerning these drugs are available to the FDA). This association does not occur, however, in non-Asian populations or patients with DRESS [1]. In whites, CBZ-induced hypersensitivity reactions are associated with the

HLA haplotype HLA-B8.1 consisting of B-0801-TNF2-DRB1*03-DQB1*02 HLA specificities [10]. In addition, the HLA-A*3101 allele has been associated with CBZ-induced hypersensitivity reactions among subjects of Northern European ancestry [1]. Nonetheless, neither of the cases reported here presented the HLA-B-0801-TNF2-DRB1*03-DQB1*02 or HLA-A*3101 allele, or indeed had any HLA alleles in common with one another. Continued genotyping of this population, however, could extend our knowledge on this gene-drug interaction leading to improved patient outcomes.

Conclusion

Our data showed that the HLA typing tested, in this case, was not a good marker for the adverse reactions observed in the subjects. Furthermore, in populations of mixed ethnicity, such as in Brazil, this procedure would be valid when data assurance on ethnicity of the patient are available, which becomes unfeasible in colonized countries by other people. In the case of Brazilian boys studied no correlation between HLA tested and literature was found. Therefore, further studies are warranted on the major histocompatibility complex to identify the causal variant(s) predisposing to serious hypersensitivity reactions to anticonvulsants in Brazilian ethnic groups.

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Table 1. **Laboratory Results During Hospitalization**

Laboratory Test	**ormal Value**	**Admission Day**		**Peak Day**		**Discharge Day**	
		Pt1	**Pt2**	**Pt 1**	**Pt2**	**Pt1**	**Pt2**
Hemoglobin (g/dL)	13.5-18.0	13.4	13.8	9.6	12	9.6	12.9
White blood cell count (× 10^9/L)	4-10	31.3	1.6	43.5	13	14.4	14.1
Eosinophils	1–6% (180–1080/mm^3)	8	14	13	9	2	1
Typical lymphocytes (%)	25–33	29	29	45	44	48	48
Atypical lymphocytes (%)	0	0	0	7	5	0	0
Platelet count (× 1000/mm3)	150–450	329	136	185	169	276	259
AST (U/L)	15–37	190	48	863	315	36	18
ALT (U/L)	30–65	250	50	631	222	103	65
GammaGT (U/L)	5–85	ND	124	1523	219	413	131

Laboratory Test	ormal Value	Admission Day		Peak Day		Discharge Day	
Alkaline phosphatase (U/L)	50–136	792	402	835	439	255	198

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GammaGT = gamma-glutamyl transpeptidase; Pt = patient; ND = no data

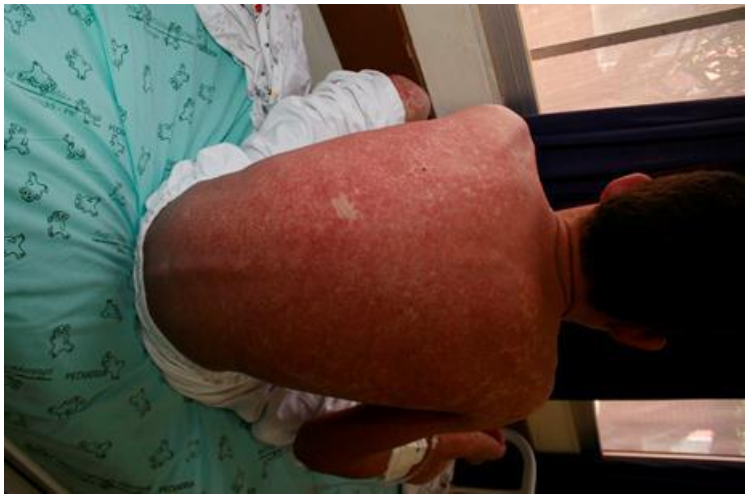

Figure 1. Urticated plaques on the back of a patient 2

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