DECREASED HYPOPROTHROMBINEMIC RESPONSE TO WARFARIN SECONDARY TO THE WARFARIN–NAFCILLIN INTERACTION

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ABSTRACT: Patients who are receiving multiple medications must be screened for significant drug interactions. The specific mechanism of a drug interaction determines whether the patient may experience a subtherapeutic effect or a potentially toxic reaction. Three cases of relative warfarin resistance, possibly related to high-dose nafcillin, are described in this report. Several reports have suggested that penicillinase-resistant penicillins, such as nafcillin and dicloxacillin, exert an important enzyme-inducing effect in patients receiving warfarin. This potential interaction must be appropriately recognized and managed in order to maintain adequate anticoagulation in this patient population.

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DRUG INTERACTIONS ARE OFTEN UNPREDICTABLE and difficult to document. If they are not detected, they can prolong and complicate hospital stay and treatment. An important mechanism for drug interaction is hepatic microsomal enzyme induction. It is well documented that the administration of drugs such as phenytoin, barbiturates, carbamazepine, and rifampin result in an increase in mixed-function oxidase enzyme activity in the liver.[1-5] Enzyme induction produces a significant increase in the metabolic clearance of drugs that are primarily metabolized by the microsomal enzyme system in the liver. These would include drugs such as warfarin, quinidine, and theophylline.[6-8] The serum concentrations of these agents may be greatly decreased secondary to this effect, resulting in a reduced therapeutic effect.

When enzyme induction occurs, the dosage of the affected drug must be increased in an attempt to maintain a therapeutic serum concentration. Also, if the enzyme-inducing drug is discontinued, the dosage of the affected drug generally should be reduced over several weeks.

Nafcillin may produce significant enzyme induction resulting in a loss of adequate warfarin anticoagulation.[9] The administration of dicloxacillin also decreases the hypoprothrombinemic response to warfarin.[10] We have demonstrated a possible association of three cases within our institution where the nafcillin–warfarin interaction has been shown to be clinically relevant.

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CASE REPORTS

CASE 1

A 61-year-old man was hospitalized for fever, chills, dizziness, and rigors. The preliminary diagnosis was either pneumonia or endocarditis. The patient underwent aortic valve replacement in 1981 with a 30-mm Medtronic aortic valve prosthesis. Since that time, the patient had been treated with warfarin sodium 5.0 mg/d with therapeutic prothrombin times (PT).

On admission, the patient's PT was 19.5 seconds (control 12.6). Blood cultures were obtained and reported positive for *Staphylococcus aureus*. A diagnosis of *S. aureus* endocarditis was made. The patient was treated with nafcillin 2 g iv q4h. Warfarin was continued at the admission dosage of 5.0 mg/d. Seven days after initiation of the nafcillin, the PT was 14.1 seconds. Over the next 29 days his PT ranged between 13.7 and 20.7 seconds, and his daily warfarin dosage requirements increased to a maximum of 17.5 mg. During the last week of nafcillin therapy, the patient received an average dose of 15.0 mg/d which maintained the PT at approximately 17.0 seconds.

Because the patient had improved clinically, cefazolin sodium 1 g iv q6h was substituted for nafcillin for the last week of treatment. The patient required 15.0 mg of warfarin daily to maintain the PTs in the range of 17.7 seconds during the first four days of cefazolin therapy. His warfarin requirements quickly declined to his prenafcillin treatment dose of 5.0 mg/d, eight days after discontinuing nafcillin therapy.

CASE 2

The patient was a 63-year-old man with previous mitral and aortic valve replacements. He had been treated with warfarin 5.0 mg/d, maintaining PTs in the range of 18.0–21.0 seconds. The admission PT was 31.0 seconds (control 11.8). Vitamin K was not administered upon admission. PT elevation was probably secondary to bacteriologic endocarditis and his associated febrile state. Warfarin was held until five days later, at which time the PT was 20.0 seconds (within the recommended range of 1.5–2.0 times control).[11]

Nafcillin 1.5 g iv q4h was initiated in response to blood cultures that grew *S. aureus* sensitive to nafcillin. Approximately five to seven days after nafcillin was initiated, the patient's PTs decreased to 13.0 seconds while on warfarin 5.0 mg/d. Despite daily 2.5-mg increases, it was not until the warfarin dosage was increased to 15.0 mg/d that the PT reached 17.0 seconds.

Following nafcillin treatment, the patient's warfarin requirements gradually declined to the prenafcillin dosage of 5.0 mg/d.

CASE 3

The patient was a 71-year-old man with a past medical history of aortic stenosis, coronary artery disease, and recent aortic valve replacement. Following the valve replacement, warfarin was initiated. Postoperatively, the patient initially displayed potentiation

of the effects of warfarin. A warfarin dosage of 2.5–5.0 mg/d resulted in PTs of 22–39 seconds.

Two weeks following surgery, the patient presented with a fever and sternal wound drainage. Cultures were obtained and reported positive for *S. aureus*. At this time, the sternal wound was opened and nafcillin 2 g iv q4h was begun. Warfarin was held when the nafcillin was initiated, but restarted on day 5 of nafcillin therapy at 5.0 mg/d. The patient received warfarin 5.0–7.5 mg/d for the next two weeks with the PTs in the range of 14–17 seconds. On day 16 of nafcillin therapy, the dosage interval was changed to every six hours. At this time, the warfarin dosage was 7.5 mg/d. This dose maintained PTs in the range of 20 seconds.

The warfarin was held a second time for six days due to a surgical procedure. It was restarted at 7.5 mg/d with a resultant PT of 15 seconds. The warfarin dosage was then increased to 10 mg to achieve PTs of 17–18 seconds. Nafcillin was discontinued on day 43. At this time, the PTs were in the range of 18–21 seconds on a warfarin dosage of 7.5–10.0 mg/d. Six days after the discontinuation of nafcillin, the patient was discharged on 5.0 mg/d. Two weeks after discharge, he was readmitted with a urinary tract infection. At this time, he was receiving warfarin 5.0 mg/d with resultant PTs of 23–26 seconds.

Discussion

Qureshi et al. reported the first case of enzyme induction and warfarin resistance with high-dose nafcillin. The patient was treated with nafcillin 2 g iv q4h while warfarin was continued at the usual dosage of 12.5 mg/d. After five days of nafcillin therapy, the patient's PT began to decrease and a relative resistance continued over the next two weeks despite an increase of his warfarin dose to 15.0 mg/d. At this time, heparin was substituted for the warfarin because of inadequate anticoagulation. After discontinuation of the nafcillin, the patient's warfarin requirements decreased to the preadmission dosage in approximately four weeks.[9]

The nafcillin-induced warfarin resistance was ascribed to an increased metabolism of warfarin in the presence of nafcillin. Warfarin's elimination half-life while the patient was on nafcillin was 11 hours; four days after discontinuation of nafcillin the half-life increased to 17 hours.[9] The pattern of warfarin resistance is consistent with enhanced drug metabolism by hepatic microsomal enzyme induction.

Our first case report is consistent with the case reported by Qureshi et al. The patient, prior to the nafcillin therapy, was maintained on warfarin 5.0 mg/d. During nafcillin therapy, the maximum warfarin requirement was 17.5 mg. Nine days after discontinuing nafcillin, warfarin requirements decreased to the prenafcillin dosage of 5.0 mg/d. Our second case report is similar in that increased warfarin requirements were necessary approximately five days after the initiation of nafcillin. Approximately one to three weeks after discontinuation of the nafcillin, the warfarin requirements returned to pretreatment levels. Although our third case report differs from the first two cases in that the patient was not stabilized on warfarin prior to nafcillin treatment, the relative resistance is still evident.

None of the three patients were receiving other medications that have been suspected or reported to cause interactions with warfarin. Other disease states which may account for the relative resistance to warfarin were unremarkable.

Summary

One of the most common clinical situations involving warfarin administration with nafcillin is in patients with prosthetic heart valves who develop *S. aureus* endocarditis or wound infections. We have observed three such cases where high-dose nafcillin therapy resulted in increased warfarin requirements. The mechanism of the interaction appears to involve hepatic microsomal enzyme induction; however, additional work will be needed to demonstrate a causal relationship. A review of the PT response and dosage requirements in these cases reveals an increase in the warfarin dose required to maintain a therapeutic effect. The increased requirements and degree of warfarin resistance are more pronounced in the first case presented. Thus, as with many other drug interactions, the degree of interaction will vary from patient to patient.

When warfarin and nafcillin are administered concurrently, PTs should be monitored daily, especially on the first three to five days after initiation of nafcillin. A decreased PT response may be seen, necessitating an increase in warfarin dosage. In addition, PTs should be monitored closely for several weeks following discontinuation of nafcillin.≏

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EXTRACTO

Los pacientes que están recibiendo terapia con varios medicamentos deben ser continuamente evaluados, debido a la posibilidad de interacciones significativas de drogas. El mecanismo específico de una interacción de drogas determina si el paciente puede experimentar un efecto subterapéutico o una reacción potencialmente tóxica. Este reporte presenta tres casos de resistencia relativa a wafarina relacionado a la administración simultánea de altas dosis de nafcilina. Varios estudios han sugerido que penicilinas resistentes a penicilinasas como nafcilina y dicloxacilina, ejercen un efecto inductor enzimático importante, en pacientes que reciben warfarina. Esta interacción potencial debe ser debidamente reconocida y tratada de manera que se mantenga la anticoagulación adecuada que requieren estos pacientes.

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RESUME

La détection d'interactions médicamenteuses significatives doit être faite chez les patients prenant plusieurs médicaments. Le mécanisme spécifique de l'interaction médicamenteuse déterminera si le patient expérimentera un effet sous thérapeutique ou une réaction potentiellement toxique. Trois cas de résistance relative à la warfarine possiblement reliés à des hautes doses de nafcilline sont décrits ici. Plusieurs comptes rendus suggèrent que les pénicillines pénicillinase-résistantes comme la nafcilline et la dicloxacilline ont un effet d'induction enzymatique chez les patients recevant de la warfarine. Cette interaction potentielle doit être reconnue et gérée dans le but de maintenir des taux d'anticoagulations adéquats pour cette population de patients.

PIERRE DION

SHORT REPORTS

FLUTAMIDE-INDUCED METHEMOGLOBINEMIA

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ABSTRACT: The authors report a case of clinical methemoglobinemia occurring one year after a patient began receiving flutamide 750 mg/d for prostate cancer with bone metastasis. The patient presented with severe cyanosis involving his lips and proximal extremities and moderate dyspnea. Methemoglobinemia was 16.2 percent of the total hemoglobin and intravenous ascorbic acid was administered. Clinical examination and laboratory analysis revealed no other cause. There was no biochemical evidence of congenital methemoglobinemia and no other regular drug use or chemical exposure was found. Moreover, clinical improvement and normalization of the methemoglobin level after the drug was discontinued is highly suggestive of flutamide-induced methemoglobinemia. Due to its chemical structure derived from anilide, flutamide may be considered as a potential methemoglobin-inducing agent.

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FLUTAMIDE is a nonsteroidal antiandrogenic drug, considered as a suitable alternative to other systemic antiandrogenic treatment in patients with advanced prostatic cancer.[1] Even though drug labeling points to the possible occurrence of methemoglobinemia, no clinically symptomatic case has so far been reported.

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CASE REPORT

In November 1988, prostate cancer with bone metastasis was diagnosed in an 80-year-old white man. The initial treatment included orchidectomy and flutamide 750 mg/d. Two months later, the clinical efficacy of this treatment was demonstrated by the relief of bone pain, and improved serum prostate acid phosphatase level and bone scan. In December 1989 the patient experienced an episode of mild dyspnea of unknown origin that was associated with mild cyanosis. On March 23, 1990, the patient was hospitalized with severe cyanosis involving his lips and the proximal extremities and stage II dyspnea (New York Heart Association criteria, i.e., dyspnea induced by moderate exercise). Clinical examination produced no evidence of pulmonary or cardiac failure, and the normal chest X-ray and arterial blood gas analysis suggested a metabolic cause for the cyanosis. The hemoglobin was 120 g/L and hematocrit 0.357. Other laboratory analyses, including white cell count, hepatic transaminases and bilirubin, blood urea nitrogen, and serum electrolytes were within normal range. Further investigation found the concentration of methemoglobin equal to 16.2 percent of the total hemoglobin (normal value <1 percent) as measured using spectrophotometry. The possibility of acute flutamide-induced methemoglobinemia was suspected; the drug was immediately discontinued and ascorbic acid 3 g/d iv was begun.[2] Progressive recovery was observed and clinical cyanosis and dyspnea greatly improved within ten