Potentiation of Vitamin K Antagonists by High-Dose Intravenous Methylprednisolone

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Background: Oral anticoagulants and pulse high-dose intravenous methylprednisolone are often administered concomitantly, but no data on potential interactions are available.

Objective: To assess possible potentiation of oral anticoagulation by high-dose intravenous methylprednisolone.

Design: Prospective cohort study.

Setting: University hospital in Paris, France.

Patients: 10 consecutive patients concomitantly receiving methylprednisolone and oral anticoagulants (fluindione and acenocoumarol) and 5 consecutive controls receiving methylprednisolone alone.

Measurements: Serial determinations of the international normalized ratio (INR) and clotting factors during administration of pulse methylprednisolone. The total plasma fluindione concentration was determined in 3 patients.

Results: The mean INR was 2.75 (range, 2.02 to 3.81) at baseline and increased to 8.04 (range, 5.32 to 20.0) after methylprednisolone administration. Plasma fluindione concentrations and the INR increased after methylprednisolone administration. Methylprednisolone alone did not increase prothrombin time.

Conclusions: The action of oral anticoagulants is potentiated by intravenous high-dose methylprednisolone. The INR should be monitored daily during concomitant administration of these medications.

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Pulse high-dose intravenous methylprednisolone is widely used for the treatment of flares in inflammatory and autoimmune diseases (1). Most of these diseases carry a risk for venous and arterial occlusion (2–4). In addition, patients may have individual indications for oral anticoagulation that are independent of inflammatory disease, such as atrial fibrillation and mechanical prosthetic heart valves. Therefore, oral anticoagulants and methylprednisolone are often administered concomitantly in clinical practice.

In early studies, oral anticoagulants had both enhanced (5) and diminished effects (6, 7) when given concurrently with oral corticosteroids. Corticosteroids are not thought to potentiate oral anticoagulants (8).

In a patient receiving oral anticoagulation, we observed a sharp increase in the international normalized ratio (INR) after concomitant administration of methylprednisolone. This observation, and the lack of relevant published data, prompted us to conduct a prospective study of the potential interaction of methylprednisolone with oral anticoagulants.

Methods

Patients

We studied 10 consecutive patients who were referred to the internal medicine department of Pitié-Salpêtrière Hospital in Paris, France. The 4 women and 6 men (mean age, 51 years [range, 20 to 79 years]) were taking oral anticoagulants and received methylprednisolone for giant-cell arteritis ($n = 2$), autoimmune thrombocytopenic purpura ($n = 2$), vasculitis ($n = 3$), multiple myeloma ($n = 1$), lupus flare ($n = 1$), or mediastinal fibrosis ($n = 1$). Methylprednisolone was given in the form of 1 g or 500 mg of hemisuccinate methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Saint-Quentin en Yvelines, France) reconstituted in 5% dextrose in water (total volume, 250 mL) and was infused intravenously over 1 hour. All 10 patients were taking vitamin K antagonists (fluindione [$n = 8$] and acenocoumarol [$n = 2$]) for atrial fibrillation ($n = 3$), the antiphospholipid syndrome ($n = 3$), thromboembolic events ($n = 2$), distal limb ischemia ($n = 1$), or the superior vena cava syndrome ($n = 1$). Daily doses were 4 mg of acenocoumarol ($n = 2$) and 5 mg ($n = 1$), 10 mg ($n = 2$), 20 mg ($n = 3$), 25 mg ($n = 1$), or 40 mg ($n = 1$) of fluindione; these doses

had not been increased in the 10 days before administration of the first methylprednisolone pulse. Except for the first patient, informed consent was obtained in each case before study enrollment.

The control group consisted of five consecutive patients (mean age, 50 years [range, 21 to 80 years]) who were receiving methylprednisolone for giant-cell arteritis ($n = 2$), lupus flare ($n = 1$), idiopathic retroperitoneal fibrosis ($n = 1$), or Crohn disease ($n = 1$). Controls did not receive oral anticoagulants before or during methylprednisolone administration.

All of the cases were reported to the Paris-Pitié-Salpêtrière regional pharmacovigilance center.

Concomitant Medications

Concomitant medications were screened for drugs known to potentiate oral anticoagulants (8, 9). Two patients were receiving concomitant amiodarone therapy, but the doses had not been modified during the 6 months before the study began and were not modified during the study. Three patients were receiving acetaminophen, but the weekly dose was less than 4550 mg (the minimum dose that has been found to increase the INR) during the week before methylprednisolone administration and throughout the study (10).

Clotting Tests

The prothrombin time, interpreted as the INR, was measured by using the Simplastin Excel S reagent with an international sensitivity index of 1.31 (Organon Teknika Corp., Durham, North Carolina). Factors II, VII, IX, and X were routinely measured by using an STA IX analyzer (Diagnostica Stago, Asnières-sur-Seine, France), as described elsewhere (11). Levels of protein C and free protein S were assayed by using an amidolytic method (Berichrom Protein C, Dade Behring, Liederbach, Germany) and a procoagulant method (Protein S Reagent, Dade Behring), respectively, on a Behring Coagulation Timer (Dade Behring). Total (free and protein-bound) fluindione levels were assayed by using high-performance liquid chromatography, as described elsewhere (12).

Results

International Normalized Ratio after Administration of High-Dose Intravenous Methylprednisolone

For all patients, the target INR was 2.0 to 4.0. The INR was checked during the 12 hours before methylprednisolone infusion. At baseline, the mean INR was 2.75 (range, 2.02 to 3.81). In all patients, the INR increased to a mean of 8.04 (range, 5.32 to 20.0) after methylprednisolone administration (**Figure 1**). The maximum increase in the INR occurred after a mean of 92.7 hours (range, 29 to 156 hours). Because the INR reached life-threatening levels in five patients (patients 1, 2, 4, 6, and 8), we administered vitamin K, which decreased the INR in 4 to 12 hours (**Figure 1**). In four other patients (patients 3, 5, 7, and 9), oral anticoagulation was discontinued and the INR returned to baseline in 36 to 48 hours (**Figure 1**).

Levels of protein C; free protein S; and vitamin K–dependent factors II, VII, IX, and X decreased as the INR increased. However, levels of factor V remained normal in every case (data not shown).

International Normalized Ratio after Methylprednisolone Alone

To determine whether INR elevation was caused by the action of methylprednisolone on clotting factors, we assessed the prothrombin time in five consecutive controls who received methylprednisolone (1 g/d for 3 days) without concomitant oral anticoagulation. The prothrombin time was checked every day and remained stable for 7 days after the first dose of methylprednisolone was administered (**Figure 2**).

Elevation of the International Normalized Ratio after Concomitant Administration of Methylprednisolone and Oral Anticoagulation

To rule out in vitro interference between methylprednisolone and INR reagents, we collected plasma from nine patients who were being treated with fluindione and added methylprednisolone at concentrations of 0 mg/L, 5 mg/L, and 20 mg/L (based on the peak concentration of methylprednisolone in vivo in patients treated with methylprednisolone [13]). The resulting INRs were not influenced by the baseline INR or by the dose of methylprednisolone added (data not shown).

Total plasma fluindione concentrations were serially assayed in three patients (patients 6, 8, and 10). Fluindione concentrations and the INR always increased after methylprednisolone administration (**Figure 1**).

Discussion

To determine whether methylprednisolone potentiated oral anticoagulation, we studied variations of the INR in 10 consecutive patients who were taking oral anticoagulants and received methylprednisolone concomitantly. The INR increased sharply, exceeding 6.0 in almost all patients. In contrast, methylprednisolone alone did not interfere with clotting factors (prothrombin time). These results suggest that INR elevation was due to potentiation

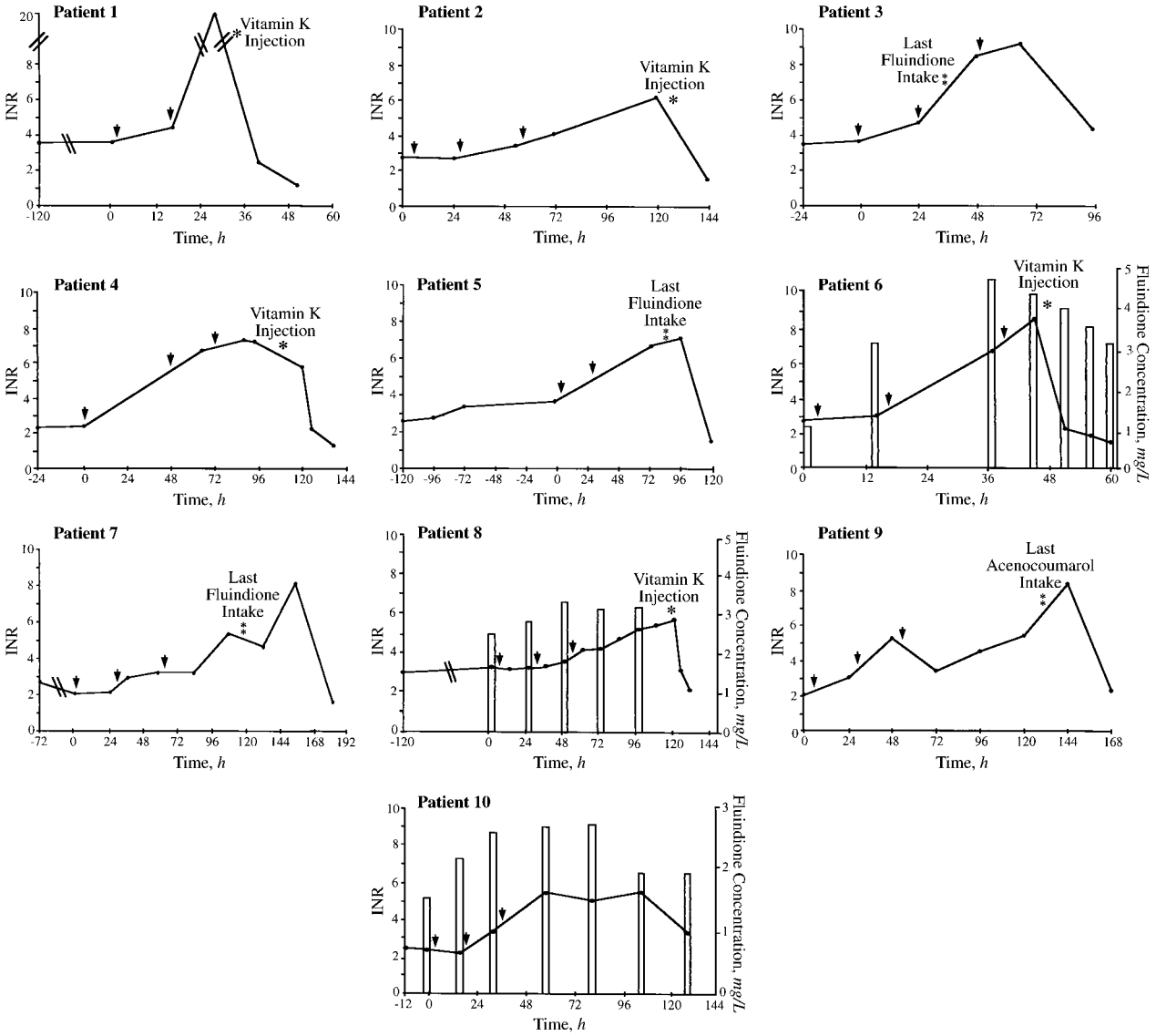

Figure 1. Potentiation of vitamin K antagonists by intravenous high-dose methylprednisolone in patients 1 through 10. Arrows indicate administration of pulse intravenous high-dose methylprednisolone; bars indicate total fluindione concentration; solid lines indicate the international normalized ratio (*INR*).

of oral anticoagulation by methylprednisolone. Although no bleeding complications occurred in this small series, the INR elevation was severe enough to warrant vitamin K supplementation or withdrawal of the vitamin K antagonist, and we were therefore unable to observe the maximum potential increase in the INR.

Our data are in keeping with those of Kaufman (14), who described two patients with multiple sclerosis who were receiving warfarin: one for a prosthetic valve and one for pulmonary embolism. In these patients, the INR reached 10.0 and 12.0, respectively, after methylprednisolone administration. Of note, two patients in our study received acenocoumarol, a coumarin congener that chemically differs from warfarin only by its nitro group at the para position in the phenyl ring.

Although our study included a small number of patients, it is unlikely that the INR increased because of spontaneous fluctuations in each patient's response to oral anticoagulants. The INR reached 6 in almost all of our consecutive patients; however, in a recent study of 29 000 INRs observed during a 6-month period (15), only 85 exceeded 6.0. Furthermore, our patients did not have any of the conditions reported to increase the INR, such as alcoholism, liver disease, frequent modification of oral anticoagulant dose, and recent withdrawal or initiation of medications known to interact with oral anticoagulants. In a study of 55 625 INRs in which 131 patients had INRs that exceeded 8.0, one of two hemorrhage-related deaths involved a patient taking warfarin who was receiving high-dose steroids for vasculitis (16).

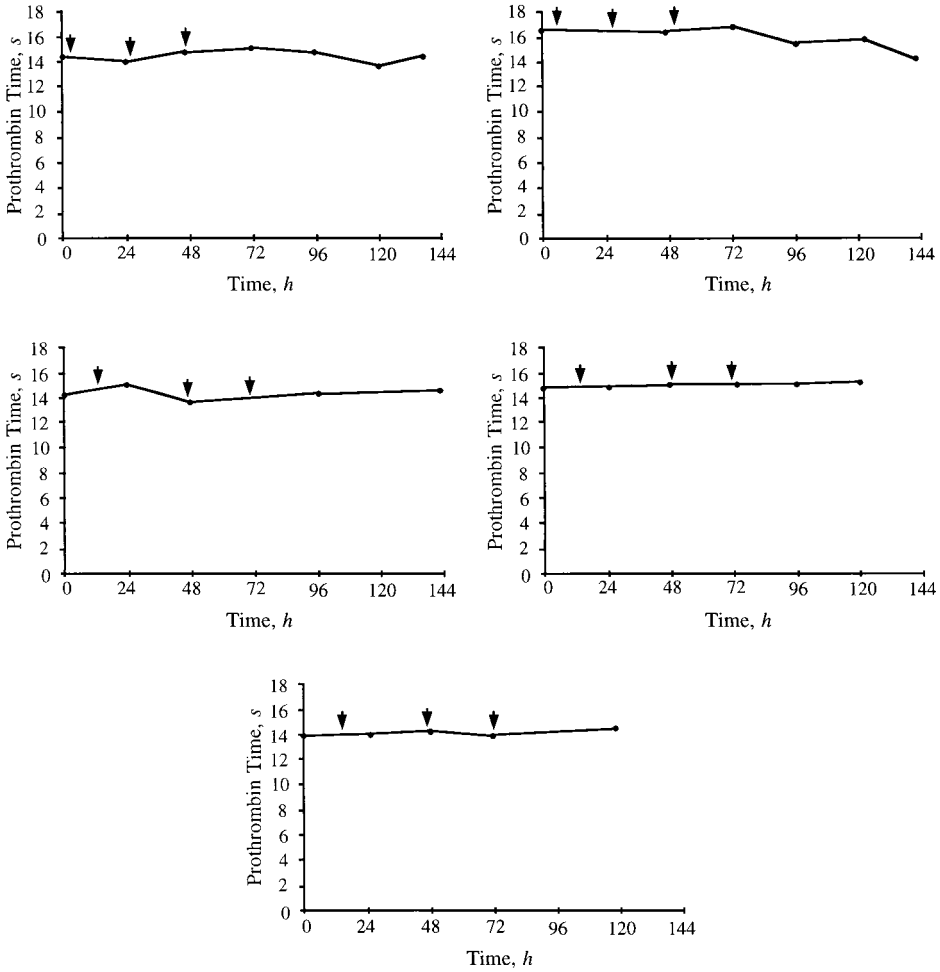

Figure 2. Lack of effect of intravenous high-dose methylprednisolone alone on prothrombin time in five controls. Arrows indicate administration of pulse intravenous high-dose methylprednisolone.

Although the precise mechanism of the interaction between methylprednisolone and oral anticoagulants is unclear, several lines of evidence strongly suggest that it is due to inhibition of oral anticoagulant catabolism by high-dose methylprednisolone. First, the increase in the INR observed after methylprednisolone administration occurred through a vitamin K–dependent pathway. The INR increased regardless of the anticoagulant used (acenocoumarol, warfarin, or fluindione, a noncoumarin indanedione anticoagulant that is common in Europe). In addition, this increase was rapidly reversed by administration of vitamin K (14). Second, because oral anticoagulants are almost completely absorbed from the gastrointestinal tract (9), it is unlikely that elevated fluindione concentrations were due to increased absorption. Third, because we measured total fluindione, it is unlikely that the elevated concentrations resulted from a change in the ratio between free and protein-bound fluindione. Fourth, methylprednisolone inhibits the cytochrome P450 enzyme system (17), which is involved in the metabolism of oral anticoagulants (18). It is therefore possible that high-dose methylprednisolone potentiates vitamin K antagonists by inhibiting their cytochrome P450–dependent catabolism.

Our series and the two cases reported by Kaufman (14) reflect the diverse conditions that can lead to concomitant administration of oral anticoagulants and methylprednisolone in clinical practice. Some examples are cancer, transplantation, multiple sclerosis, and various rheumatic diseases. Physicians must be aware that intravenous high-dose methylprednisolone can cause life-threatening potentiation of oral anticoagulation and that the INR must be monitored daily during combined administration. The risk may be severe enough to warrant reducing the oral anticoagulant dose before administering methylprednisolone.

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