Accidental Over-Anticoagulation: Substitution Error by a Foreign Pharmacy

Suthida Suwanvecho and J Robert Baker

OBJECTIVE: To describe an episode of inadvertent and excessive anticoagulation caused by mistaken substitution of medication by a pharmacy outside the US.

CASE SUMMARY: A 57-year-old white woman was found to have profound prolongation of her prothrombin time (56.9 sec) and international normalized ratio (22.18), with other coagulation parameters relatively normal. She had no prior history of bleeding diatheses and was not taking any prescribed anticoagulants. Her coagulopathy rapidly corrected with the administration of fresh frozen plasma and vitamin K. After her medications were visually inspected, it was discovered that she had purchased her prescription medications from a pharmacy in Mexico and that she inadvertently had been taking a preparation of warfarin (proprietary name in Mexico, "Romesa") instead of the prescribed ramipril for her hypertension (proprietary name in Mexico, "Ramace"). After removal of the incorrect medication, she experienced no further prolongation of her coagulation parameters.

DISCUSSION: Medication errors contribute significantly to adverse events for patients. The frequency of different types of medication errors is reviewed, and problems specific to the use of warfarin are detailed. Circumstances that might lead to a patient seeking prescription medication outside of the US are also discussed.

CONCLUSIONS: The acquisition of prescription medications from pharmacies outside of the US can have adverse consequences, especially if the foreign name of the medication is different from its American name, while sounding similar to other medications that also might be dispensed in foreign pharmacies.

KEY WORDS: medication errors, warfarin.

Ann Pharmacother 2000;34:1132-5.

Errors in prescribing and dispensing of medications are known to cause significant patient morbidity and mortality. The risk of complications from errors is heightened when a medication with a narrow therapeutic window such as warfarin is used, even when it is prescribed and administered appropriately.

We describe a woman who mistakenly obtained warfarin in the place of an antihypertensive medication from a pharmacy outside of the US, likely due to the similarity of their foreign proprietary names and their strength.

CASE REPORT

A 57-year-old white woman presented to the internal medicine ambulatory clinic with a four-day history of bloody urine. She had no dysuria, increased urinary frequency, or fever. She reported scant blood in expectorated sputum and had noticed an increased tendency for bruising in her extremities over the past few weeks.

Past history was remarkable for hypertension (treated with ramipril 5 mg/d and atenolol 50 mg/d), diabetes mellitus type 2 (controlled with glyburide 20 mg/d and metformin 850 mg tid), and diabetes-induced peripheral neuropathy (treated with gabapentin 300 mg qhs, amitriptyline 100 mg/d, and meprobamate 400 mg tid). She had undergone coronary artery bypass grafting four years previously and was free of anginal symptoms while taking isosorbide mononitrate 30 mg/d. She had hypothyroidism (treated with L-thyroxine 0.05 mg/d). She was placed on warfarin therapy after bypass grafting, maintaining adequate anticoagulation on an alternating dosage of 2.5 mg/1.25 mg every other day. Anticoagulation with warfarin had been discontinued one year before her presentation.

Initial evaluation revealed a woman comfortable at rest. Her BP was 126/64 mm Hg and HR was 82 beats/min. Multiple ecchymoses were present on her distal extremities, but no active bleeding was clinically apparent. Urinalysis found >20 RBC/hpf, with no white blood cells seen. Urine glucose was 4+, but urine ketones were negative. Serum glucose was 182 mg/dL (normal range 80–126), hemoglobin was 14.2 g/dL (13.0–17.3), and platelet count was $380 \times 10^3/mm^3$ (140–400). Coagulation studies showed prothrombin time (PT) 56.9 sec (10.4–12.6), international normalized ratio (INR) 22.18, and partial thromboplastin time (PTT) 90.6 sec (23.0–31.8). Fibrinogen was elevated at 585 mg/dL (200–400). Fibrin degradation products were <10 µg/mL (<10). Both PT and PTT returned to normal ranges after mixing with normal plasma, indicating that the cause of her coagulopathy was a deficiency in clotting factors and not due to the action of a direct anticoagulant.

Because of significant hematuria, she was given 6 units of fresh frozen plasma. Oral phytonadione 10 mg was given daily for five days. The PT and INR returned to normal range after re-

Author information provided at the end of the text.

ceiving this therapy; on hospital day 3, PT was 11.8 sec and INR was 1.00.

In the course of evaluation, we examined the medications that our patient had brought from home. She said that she had gone to Mexico to obtain her prescription medications because they were less expensive there. Typically, she would take a list of her prescription medications into one of several pharmacies along the Texas–Mexico border. There, the pharmacist would give her boxes of medication after first comparing the US proprietary name with the Mexican equivalent. She was not required to present the actual written prescriptions in any of the Mexican pharmacies prior to receiving her medications, and no formal counseling about these medications was provided. On returning home, she would take the pills purchased in Mexico out of their packaging and store them in bottles obtained when she previously had purchased those medications in a US pharmacy. She had obtained a supply of all of her prescription medications in Mexico three months prior to this hospitalization.

She had several boxes of medication that she identified as her blood pressure medication. Included among these were boxes labeled as both "Ramace 5 mg" and "Romesa 5 mg" (Figure 1). Closer inspection of the boxes found that the medication with the proprietary name Ramace was generic ramipril, and these boxes were hand-labeled as "Altace," as had been prescribed for her hypertension. The box with the proprietary name Romesa also bore the handwritten name "Altace," but this medication was discovered to be generic "warfarina." This error in labeling was subsequently corrected by the authors, as seen in Figure 1. The tablets were similar in size and shape; Ramace was white in color, while Romesa was light blue.

Figure 1. Comparison of Romesa and Ramace boxes.

We determined that our patient had mistakenly been given and was taking warfarin instead of the prescribed ramipril. Our patient had open boxes of both Ramace and Romesa, and she had placed tablets of each into the bottle previously containing Altace. It was unclear when the substitution had occurred or how much warfarin she might have taken over time.

After ensuring that her coagulation profile remained normal for another day, our patient was discharged to complete the five-day course of vitamin K at home. She was given a new prescription for ramipril and encouraged to fill it in a local pharmacy. She was seen in follow-up 10 days later, at which time her PT and INR were normal at 11.2 sec and 0.90, respectively. She had no further bleeding complications.

Discussion

Problems associated with errors made in the prescribing and dispensing of medications are well reported. Lesar et al.[1] reported that more than 11 000 errors in medication prescribing were discovered through a nine-year surveillance period in a teaching hospital, and that the incidence of these errors had increased almost four-fold during the duration of the study. One survey[2] found that 82% of Australian pharmacists believed that medication dispensing errors were increasing, and cited as possible contributing factors high prescription volumes, pharmacists' overwork and fatigue, and confusing drug names. Inadvertent medication substitution has been shown to occur, at least in part, due to the illegible handwriting of some physicians.[3] Our report, however, is believed to be the first report of an adverse event resulting from a patient obtaining an incorrect prescription medication from a pharmacy outside the US.

The potential for a medication error due to unintended substitution was not immediately recognized, as the American proprietary names of Altace and Coumadin are much less similar to each other than are the Mexican counterparts of Ramace and Romesa. The tablets of each of these medications obtained in Mexico had slightly different colors, but both were significantly different than the red capsule formulation of Altace 5 mg that is available in the US. With the increased use of generic substitution, it is not uncommon for a patient to be given pharmacologically equivalent forms of the same medication that may differ in size, shape, and color, even when the prescriptions are filled by US pharmacies.

The level of anticoagulation excess induced by the medication error in our patient was extensive. The response to therapeutic warfarin use is well recognized to have a high degree of variability. Our patient had been previously shown to be most sensitive to warfarin's anticoagulant effect, requiring only approximately one-third the usual dosage to achieve appropriate anticoagulation. The amount of warfarin our patient was inadvertently taking could have

led to the observed level of INR prolongation. The anticoagulant effect also may have been augmented by her concomitant use of glyburide and/or levothyroxine, both of which may further increase the INR in patients taking warfarin. Additionally, our patient may have had a lack of dietary vitamin K, which might have accentuated the coagulopathy induced by the inadvertent warfarin. A detailed diet history was not obtained; however, as our patient maintained normal coagulation profiles after removal of warfarin, dietary deficiency of vitamin K is less likely.

Several studies have evaluated errors made in the prescribing and dispensing of medications. Johnson et al.[4] reviewed medications prescribed at the time of hospital discharge and found that 19 of 335 prescriptions (5.7%) contained written mistakes in dosage formulation or dosing frequency. Six of the prescriptions reviewed (1.8%) contained discrepancies between the written prescriptions and the labeling on the dispensed medication bottle. Allan et al.[5] reported that 24 of 100 prescription orders filled in community pharmacies had dispensing errors, of which four were thought to be clinically significant. The method by which our patient obtained her medications has been shown to be less formal than the procedure required in US pharmacies. It is conceivable that the rate of medication error may well be higher in foreign pharmacies. To date, however, no study has evaluated the rate or type of errors made in prescriptions filled by pharmacies outside of the US.

Warfarin use has increased over the past several years, as it has been recognized that long-term anticoagulation of persons with atrial fibrillation can effect a significant decline in their risk of thromboembolic stroke. However, warfarin remains a potentially dangerous medication. The clinical effect of warfarin can be altered by changes in dietary intake of vitamin K, by the addition or deletion of other medications that are also hepatically metabolized, or by preexisting liver disease.[6] The incidence of bleeding complications with oral anticoagulation has been reported to be lower with the increasing use of the INR, but still was reported at 7.6 occurrences per 100 patient-years.[7] Deaths have been attributed to the use of warfarin.[8] The possibility of a person taking warfarin after it was mistakenly dispensed by a foreign pharmacy adds another variable to this already complex situation.

The practice of purchasing medication from pharmacies outside of the US has been studied. Casner and Guerra[9] reported that, of patients seen in a university-based internal medicine ambulatory clinic in El Paso, Texas, more than 80% describe having obtained prescription medications across the border in Juarez, Mexico, without a prescription. The lower price of the medication was an overriding factor.

Our patient did not have means for reimbursement of prescription medication costs. Although Lubbock, Texas, is more than 400 miles from Mexico, she felt that it was still economically feasible for her to obtain her prescription medications in Mexico. Based on her comparisons with US pharmacy retail prices, our patient calculated that the monthly cost of her medications would increase by 300% were she to purchase them in the US. Buying all of her prescription medications in Mexico has allowed our patient to save almost $10 000 per year. As pharmaceutical costs continue to rise, it is understandable that patients may continue to find unusual methods of acquiring their medications.

This case emphasizes the importance of careful attention to ensure that a patient is provided with the medications that have been prescribed, irrespective of where the patient might choose to fill those prescriptions. Periodic medication review, including visual inspection of agents a patient is presently taking, may reveal medication errors before an adverse event could occur. Such reviews could be accomplished through increased use of clinical pharmacists in the outpatient setting, perhaps as part of a yearly review of patient medication adherence. This should prove to be a useful adjunct to comprehensive patient care.

Summary

We report a dispensing error by a pharmacy in Mexico, which mistakenly substituted warfarin (Romesa) for ramipril (Ramace). This error led to the inadvertent excessive anticoagulation of a woman who thought she was treating hypertension. US physicians practicing in border states that can provide access to foreign pharmacies should have heightened sensitivity for the potential of this type of medication error.

Studies to quantify the rate of errors made in the filling of prescriptions by foreign pharmacies near the US border, with comparison to the error rate of nearby American-based pharmacies, would be worthwhile. This information could prove useful both for patients who might choose to fill their prescriptions outside the US and for the physicians who treat them. In the interim, physicians and pharmacists should factor this additional variable into their efforts to educate patients about the medications they take.

Suthida Suwanvecho MD, Assistant Instructor, Department of Internal Medicine, Texas Tech University School of Medicine, Lubbock, TX

J Robert Baker MD, Assistant Professor, Department of Internal Medicine, Texas Tech University School of Medicine

Reprints: J Robert Baker MD, Department of Internal Medicine, Texas Tech University Health Sciences Center, 3601 4th St., Lubbock, TX 79430, FAX 806/743-3148

References

1. Lesar TS, Lomaestro BM, Pohl H. Medication-prescribing errors in a teaching hospital. A 9-year experience. Arch Intern Med 1997;157: 1569-76.
2. Peterson GM, Wu MS, Bergin JK. Pharmacist's attitudes towards dispensing errors: their causes and prevention. J Clin Pharm Ther 1999; 24:57-71.
3. Brodell RT, Helms SE, KrishnaRao I, Bredle DL. Prescription errors. Legibility and drug name confusion. Arch Fam Med 1997;6:296-8.
4. Johnson KB, Butta JK, Donohue PK, Glenn DJ, Holtzman NA. Discharging patients with prescriptions instead of medications: sequelae in a teaching hospital. Pediatrics 1996;97:481-5.
5. Allan EL, Barker KN, Malloy MJ, Heller WM. Dispensing errors and counseling in community practice. Am Pharm 1995;NS35:25-33.

6. Brigden ML, Kay C, Le A, Graydon C, McLeod B. Audit of the frequency and clinical response to excessive oral anticoagulation in an outpatient population. Am J Hematol 1998;59:22-7.
7. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet 1996;348:423-8.
8. Reardon M, Burns B, Brewer B, O'Sullivan JP. Deaths associated with warfarin in elderly patients. Br J Clin Pract 1995;49:322-3.
9. Casner PR, Guerra LG. Purchasing prescription medication in Mexico without a prescription. The experience at the border. West J Med 1992; 156:512-6.

EXTRACTO

OBJETIVO: Describir un episodio de anticoagulación inadvertida y excesiva causada por la sustitución errónea del medicamento prescrito por una farmacia localizada fuera de los Estados Unidos.

RESUMEN DEL CASO: Una mujer de 57 años de edad se presentó a una clínica ambulatoria refiriendo sangre en la orina. Las pruebas de laboratorio reflejaron una prolongación considerable en el tiempo de protrombina (56.9 segundos) y en la razón internacional normalizada (RIN; 22.18), aunque otros parámetros de coagulación resultaron relativamente normales. La mujer no tenía historial previo de sangrado y no estaba usando ningún anticoagulante prescrito. Su coagulopatía se corrigió rápidamente con la administración de plasma fresco y vitamina K. Durante el período de evaluación, se obtuvo información de que la mujer había decidido adquirir sus medicamentos de receta en una farmacia localizada en Méjico. Al inspeccionar visualmente sus medicamentos, se descubrió que había estado tomando inadvertidamente un medicamento a base de warfarina (nombre de marca en Méjico–"Romesa") y no ramipril, el medicamento prescrito para su hipertensión (nombre de marca en Méjico–"Ramace"). Una vez descontinuado el medicamento, los parámetros de coagulación volvieron a la normalidad.

DISCUSIÓN: Los errores en medicación contribuyen significativamente a eventos adversos en los pacientes. La frecuencia con que ocurren los diferentes tipos de errores se repasa en el artículo. Se detallan problemas específicos con el uso de warfarina. Se discuten las circunstancias que pueden llevar a que los pacientes adquieran sus medicamentos fuera de los Estados Unidos.

CONCLUSIONES: La adquisición de medicamentos que requieren receta en farmacias localizadas fuera de Estados Unidos puede resultar en consecuencias adversas para el paciente, especialmente si el nombre de marca en ese pais es diferente al nombre de marca en Estados Unidos y si suena o se escribe de forma similar al nombre de otros medicamentos dispensados en esas farmacias extranjeras.

Homero A Monsanto

RÉSUMÉ

OBJECTIF: Décrire un épisode d'anticoagulation excessive par l'inadvertance d'une substitution médicamenteuse erronée dans une pharmacie d'un pays extérieur aux Etats-Unis.

RESUME DU CAS: Il a été remarqué chez une femme de 57 ans une prolongation prononcée de son temps de prothrombine (56.9 sec) et de son rapport international normalisé (RIN; 22.18), les autres paramètres de coagulation restant relativement normaux. Elle n'avait pas d'antécédents de syndrome hémorragique et ne prenait aucun anticoagulant sur prescription. Sa coagulapathie s'est rapidement corrigée par administration de plasma frais congelé et de vitamine K. On a appris qu'elle avait choisi d'acheter ses médicaments prescrits dans une pharmacie au Mexique. Ses médicaments avaient été vérifiés visuellement. On a découvert qu'elle avait pris, par inadvertance, une préparation de warfarine (nom de spécialité "Romesa" au Mexique) au lieu de ramipril qui lui avait été prescrit pour son hypertension (nom de spécialité "Ramace" au Mexique). Après l'arrêt du médicament inadéquat, elle n'a pas montré d'autre prolongation de son déséquilibre des paramètres de coagulation.

DISCUSSION: Les erreurs médicamenteuses contribuent significativement aux effets indésirables pour les patients. La fréquence des différents types d'erreurs médicamenteuses est considérée. Les problèmes spécifiques à l'utilisation de la warfarine sont détaillés. Les circonstances susceptibles d'amener un patient à chercher à se procurer des médicaments de prescription à l'extérieur des Etats-Unis sont exposées.

CONCLUSIONS: L'achat de médicaments de prescription dans des pharmacies à l'extérieur des Etats-Unis peut entraîner des conséquences néfastes, en particulier si le nom étranger du médicament est différent de son nom américain, tout en ressemblant à d'autres noms de médicaments susceptibles d'être dispensés dans des pharmacies à l'étranger.

Michel Le Duff