Fatality from Administration of Labetalol and Crushed Extended-Release Nifedipine

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OBJECTIVE: To report a case in which a crushed extended-release (XL) nifedipine tablet contributed to a patient fatality.

CASE SUMMARY: A 38-year-old woman with multiple medical problems presented to the hospital in acute respiratory distress and was diagnosed with acute pulmonary edema and pneumonia. After initial stabilization, her medications were changed to oral hydralazine, labetalol, and nifedipine XL. These medications were crushed and administered through a nasogastric tube. The patient developed worsening bradycardia with hypotension and experienced asystolic cardiac arrest. She was resuscitated; however, the following morning, another dose of labetalol and nifedipine XL was crushed and administered through the nasogastric tube. She again developed worsening bradycardia with hypotension and ultimately died.

DISCUSSION: The administration of a crushed nifedipine XL tablet resulted in the patient's severe hypotension. The concurrent administration of labetalol prevented a compensatory heart rate increase. The repeat administration of nifedipine XL in the same manner underscores a fundamental problem in healthcare worker communication and drug delivery system comprehension. Use of the Naranjo probability scale indicated a highly probable relationship between the patient's hypotension and the nifedipine and labetalol therapy.

CONCLUSIONS: Simultaneous administration of a β-blocker and a calcium-channel blocker may produce synergistic effects. The release characteristics of oral controlled-release medications are destroyed when crushed, resulting in the rapid bioavailability of the total drug amount. The importance of education and communication among nurses, physicians, and pharmacists regarding the mechanism of action of controlled-release medications and their administration needs to be emphasized.

KEY WORDS: controlled-release; nifedipine, crushed; sustained-release.

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The term "controlled release" is used to refer to a number of methods designed to modify the liberation of drug from a formulation. This terminology includes preparations labeled as "long acting," "extended," "delayed," or "sustained release." Unlike immediate-release preparations, in which the total amount of drug is rapidly available after ingestion, controlled-release formulations are designed to release specific amounts of drug over a certain time period. The major benefits include improved pharmacokinetics (e.g., less variation between peaks and troughs), less frequent dosing, and improved patient adherence. This method is currently used extensively for several different classes of medications, including antihypertensives, anticonvulsants, and analgesics.[1,2] These formulations contain a much larger total amount of drug than a single therapeutic dose of an immediate-release preparation since they are expected to maintain a therapeutic concentration for prolonged periods.

The specialized structure of these tablets or capsules, commonly referred to as the "matrix," is what provides their unique release characteristics and is destroyed upon crushing of the tablet. Ingestion of the crushed form provides a much larger amount of drug for immediate absorption and has the potential to cause toxicity. A specific formulation of OxyContin (160 mg) was removed from the market due to widespread abuse through consumption of the crushed tablet to provide a significantly greater high.[3,4]

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We report a case in which a crushed extended-release nifedipine tablet contributed to a fatality.

Case Report

A 38-year-old woman presented to the emergency department with the chief symptom of shortness of breath that woke her from sleep in the early morning. Her medical history was significant for asthma, HIV, hypertension, endstage renal disease, and tobacco use. Her antihypertensive medications included clonidine 0.2 mg orally 3 times a day, extended-release nifedipine 90 mg orally once daily, metoprolol 100 mg orally twice daily, and furosemide 60 mg orally twice daily.

On examination, she was anxious, diaphoretic, speaking in partial sentences, and using accessory muscles of respiration. Her vital signs were T 36.3 ˚C, BP 180/110 mm Hg, HR 143 beats/min, RR 36 breaths/min, and O_2 saturation 91% while receiving a nebulized albuterol treatment. During a head and neck examination, dry mucous membranes and jugulovenous distension were noted. Bilateral rales and wheezing were heard on lung auscultation. She was tachycardic with no appreciable murmurs, rubs, or gallops. On examination, her abdomen was nontender and nondistended, and bowel sounds were normal. Examination of her extremities showed 3+ pitting edema up to her ankles. Neurologic examination showed nonfocal changes. A chest X-ray revealed bilateral infiltrates.

Presumptive diagnoses of acute pulmonary edema and pneumonia were considered, and the patient was started on intravenous nitroglycerin, furosemide, and levofloxacin. She was also treated with oxygen, nebulized albuterol, and intravenous methylprednisolone for bronchospasm. Her clinical condition improved over the next several hours, and she was admitted to the intensive care unit. The patient began experiencing a headache while receiving the nitroglycerin infusion, and her blood pressure remained elevated. She refused further treatment with nitroglycerin, and an intravenous labetalol infusion was started. While in the intensive care unit, she experienced a generalized seizure and was intubated. A computed tomography scan of her head was negative for any acute intracranial event. She was given a loading dose of phenytoin. The labetalol infusion was replaced with intravenous nitroprusside, which ultimately gained control of the hypertension.

Intravenous vasodilator therapy was tapered to discontinuation by the following morning, and the patient was started on hydralazine 50 mg orally 3 times a day, labetalol 600 mg orally twice daily, and extended-release nifedipine 90 mg orally once daily. All of the medicines were crushed by the nurse in order to be administered through a nasogastric tube. The patient became progressively more bradycardic until she developed asystole. She was successfully resuscitated with intravenous epinephrine and atropine and placed on dopamine, norepinephrine, and dobutamine infusions. The norepinephrine and dopamine infusions were tapered off; however, dobutamine was continued. Her labetalol dose was decreased to 200 mg.

The following morning, she received labetalol 200 mg and extended-release nifedipine 90 mg, which were again crushed by the nurse and administered through a nasogastric tube. The patient again developed progressively worsening junctional bradycardia and hypotension and was restarted on dopamine and norepinephrine infusions. Over the next 2 hours, 2 doses of a calcium gluconate 10% preparation (10 mL followed by 4 mL), 1 mg of glucagon, and a fluid bolus were given, with little effect. She experienced another cardiac arrest, which resolved when chest compressions and an external pacemaker were applied. Ten minutes later, her pulse was lost again but she was resuscitated with external pacing along with 2 mg of epinephrine and atropine. The patient's condition continued to deteriorate. Approximately 30 minutes later, she was given another 10 mL of calcium gluconate (10%), 10 mL of calcium chloride (10%), 3 mg of glucagon, and a fluid bolus. Despite these interventions, along with multiple high-dose vasopressor therapies, the patient experienced cardiac arrest again approximately 1 hour later and died.

Discussion

Controlled-release drug formulations are designed to alter the release characteristics of a drug within a product formulation. The purpose is usually to provide a therapeutic amount of drug over an extended time period. There are a number of delivery systems employed for this function: dissolution, diffusion, osmotic, ion exchange resins, and transdermal. Controlled-release medications may employ 1 or more of these systems.

Controlled-release drugs delivered by dissolution are generally classified as either encapsulated or matrix based.[5-7] Encapsulated medications consist of a capsule containing many small beads with coatings of variable thickness. As the coating dissolves, drug is released. This distribution of beads with coatings of variable thickness ensures a steady release of drug over a given time period. Matrix-based formulations consist of drug uniformly distributed within a water-soluble carrier. As the carrier dissolves, drug is released. Diffusion-based systems are either reservoir (membrane) or matrix based. Reservoir systems contain a central core of drug surrounded by an insoluble membrane. Drug diffuses out of the core and across the membrane after contact with gastrointestinal fluid. Drug may also be distributed throughout a water-insoluble polymeric substance. After ingestion, drug dissolves or diffuses out of the carrier polymer and is available for absorption.

Drug release may also be controlled through generation of osmotic pressure. Mini-osmotic systems contain drug separated by a membrane from an osmotically active substance.[5,7] Drug is forced through a channel as the osmotic compartment swells after ingestion of the drug. Elementary osmotic formulations contain an osmotic core (which also contains drug) that swells and subsequently releases drug through a channel into the intestinal lumen. Ion-exchange resins contain drug that is exchanged for elemental ions within the gastrointestinal tract.[5] Transdermal preparations contain drug that is slowly absorbed across the epidermis. All of these systems employ specifically designed mechanisms to ensure a slow but steady release of drug over a specific time interval.

There are currently a large number of medications available in controlled-release formulations.[1,2] Benefits of using these drugs include less frequent dosing, which probably facilitates patient adherence. However, if administered incorrectly, there is a possibility of causing serious harm.[1-4] The potential to cause harm will depend considerably on the class of medication. Use of the Naranjo probability scale[8] indicated a highly probable relationship between this patient's hypotension and her nifedipine and labetalol therapy.

Most commonly used calcium-channel blocking drugs exert their effects through antagonism of L-type calcium channels.[9-12] This blockade ultimately results in decreased intracellular concentrations of calcium needed for myocardial inotropy, heart rate, and atrioventricular conduction. Specific effects of these agents vary in regard to the particular class of calcium-channel antagonist. Nifedipine is a dihydropyridine, which has as its primary effect relaxation of peripheral vascular smooth muscle. However, the combination of calcium-channel antagonists and β-blockers may be synergistic in their negative effects on dromotropy, chronotropy, and inotropy.[13,14] Coadministration of a β-blocker with nifedipine may inhibit the compensatory

sympathetic outflow normally seen in isolated nifedipine toxicity.[14,15]

Summary

Controlled-release drug preparations contain significantly larger amounts of drug than do their immediate-release counterparts. The matrix containing the drug is actually a highly specialized delivery system that is destroyed upon crushing. Critically ill patients who are incapable of independent consumption of their medication rely on administration by hospital staff. Errors that contributed to our patient's death occurred on multiple levels. The physician failed to realize that all solid oral medications given to an intubated patient would have to be crushed for administration through a feeding tube. The pharmacy did not register the potential problem with filling this order for a patient in the intensive care unit. Finally, the nurse who crushed and administered the medications did not understand the principles and characteristics of extended-release medications. There is a need for continued education about these products and their proper administration at the level of the physician, pharmacist, and nursing staff. Incorrect administration of controlled-release formulations may result in significant harm.

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EXTRACTO

OBJETIVO: Informar sobre un caso donde el administrar una tableta triturada de nifedipina de liberación prolongada contribuyó a la muerte de un paciente.

RESUMEN: Una mujer de 38 años, con múltiples problemas médicos, se presenta al hospital con dificultad respiratoria y se le diagnostica edema pulmonar agudo y pulmonía. Luego de estabilizar al paciente, se realiza un cambio en sus medicamentos y la paciente comienza a recibir hidralazina, labetalol y nifedipina de liberación prolongada por la vía oral. Estos medicamentos se trituraban y se administraban por el tubo nasogástrico. La paciente desarrolló bradicardia con hipotensión y sufrió un arresto cardiaco asistólico. La paciente fue resucitada, sin embargo la mañana siguiente se volvieron a administrar por el tubo nasogástrico dosis trituradas de labetalol y de nifedipina de liberación controlada. La paciente volvió a desarrollar bradicardia e hipotensión y finalmente murió.

DISCUSIÓN: La administración de una tableta triturada de nifedipina de liberación prolongada causó hipotensión severa en esta paciente. La administración concurrente de labetalol evitó el mecanismo compensatorio de aumentar la frecuencia cardiaca. El volver a administrar nifedipina en la misma forma la mañana siguiente, enfatiza un problema fundamental en la comunicación y el entendimiento del sistema de dispensación de medicamentos en los trabajadores de servicios de salud. El uso de la Escala Naranjo de Probabilidad de Reacciones Adversas indica una relación de alta probabilidad entre la hipotensión ocurrida en el paciente y su terapia con nifedipina y labetalol.

CONCLUSIONES: La administración simultanea de un bloqueador beta y un bloqueador de los canales de calcio puede producir un efecto sinergista. Las características de liberación de medicamentos con una presentación de liberación controlado se pierden al triturar la tableta. Esto puede resultar en una biodisponibilidad más rápida de la cantidad total del medicamento. Hay que enfatizar la importancia de la educación y comunicación entre enfermeras, médicos y farmacéuticos sobre el mecanismo de acción de medicamentos de liberación controlada y su administración.

Annette Pérez

RÉSUMÉ

OBJECTIF: Présenter le cas d'un décès où l'administration d'un comprimé écrasé de nifédipine à libération prolongée (XL) a contribué au décès.

RÉSUMÉ DU CAS: Une femme de 38 ans, présentant de nombreux problèmes médicaux, s'est présentée à l'hôpital en détresse respiratoire aiguë. Un œdème pulmonaire et une pneumonie ont été diagnostiqués. Après stabilisation, sa médication été modifiée pour inclure l'hydralazine, le labétalol, et la nifédipine XL par voie orale. Ces médicaments ont été écrasés afin de permettre l'administration par le tube naso-gastrique. La patiente a présenté une bradycardie progressive associée à de l'hypotension et a fait un arrêt cardiaque. Elle fut réanimée, mais le lendemain une autre dose de labétalol et de nifédipine

XL écrasée ont été administrées par le tube naso-gastrique. La patiente a de nouveau présenté une bradycardie avec hypotension dont elle est finalement décédée.

DISCUSSION: L'administration de nifédipine XL écrasée a causé une hypotension sévère chez cette patiente. L'administration concomitante de labétalol a empêché une tachycardie compensatoire. La répétition de l'administration de ces médicaments révèle un problème fondamental de communication entre les professionnels de la santé et de compréhension des dispositifs d'administration des médicaments. L'utilisation de l'algorithme d'imputabilité des effets indésirable de Naranjo a permis de conclure à une forte probabilité de relation entre l'hypotension de la patiente et le traitement à la nifédipine et au labétalol.

CONCLUSIONS: L'administration simultanée d'un bloquant bêta et d'un bloquant des canaux calciques peut produire un effet synergique. Les caractéristiques du système de libération continue sont altérées lorsque le comprimé est écrasé, générant ainsi rapidement de fortes concentrations systémiques. L'importance de l'enseignement et de la communication entre infirmières, médecins, et pharmaciens concernant les mécanismes d'action des formes à libération continue et leur administration est mise en évidence par ce cas.

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