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Drug-Induced Acute Kidney Injury: A Standardized Patient Case for Clerkship Students

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Abstract

Introduction: Drug-induced nephrotoxicity is a common yet preventable cause of acute renal failure. With the upward trend of prescription and over-the-counter medication use, it has become increasingly important for health care professionals to not only be able to identify acute renal failure precipitated by medications, but also to recognize medications that are eliminated by the kidneys and adjust dosages accordingly to prevent further damage. **Methods:** In this activity, third-year clerkship medical students are presented with a standardized patient portraying an acute medical problem in which students must ascertain the underlying cause of the problem and draw from their knowledge of pharmacology, pharmacokinetic principles, and clinical therapeutics to develop a plan to address the patient's medical concerns. **Results:** We found that few students were able to identify the underlying cause of the patient's acute condition, and none were successful at applying pharmacokinetic principles appropriately. **Discussion:** Implementing this case with third-year medical students has identified the need to revisit pharmacokinetic principles in an applied setting. As a result, this topic is being added to a course that highlights the relevance of basic sciences in clinical contexts for clerkship students.

Keywords

Clerkship, Standardized Patient, Pharmacokinetics, Pharmacology, Acute Kidney Failure, Renal Injury, Drug-Induced Nephropathy, Problem-Solving

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Educational Objectives

By the end of this standardized patient case, students will be able to:

1. Assess laboratory values, medications, and patient symptoms to identify acute kidney injury.
2. Communicate the cause of the patient's symptoms and management plans to the patient.
3. Apply pharmacokinetic principles of clearance and half-life to resolve medication-related concerns.

Introduction

Drug-induced nephrotoxicity (DIN) is relatively common. DIN accounts for 7% of all drug toxicities and 20% to 30% of acute renal failures among inpatients.[1,2] Nonsteroidal anti-inflammatory drugs (NSAIDS), angiotensin converting enzyme inhibitors (ACEI), and anti-infective agents are commonly implicated in many incidents of DIN.[3] Since more than 50 million Americans are using NSAIDs, and with lisinopril being one of the most commonly prescribed antihypertensives, it is not surprising that DIN is suspected in 20% of patients hospitalized for acute kidney injury.[4-6]

Manifestations of DIN can include acid-base abnormalities, electrolyte disturbances, urine sediment abnormalities, proteinuria, pyuria, and even hematuria. However, the most common manifestation of DIN is a decrease in glomerular filtration rate, manifesting as a rise in serum creatinine and blood urea nitrogen, and a corresponding temporal relationship with a potentially nephrotoxic drug. DIN is consistent with acute renal failure, which is an abrupt and sustained decrease in glomerular filtration, urine output, or both. In hospital settings, routine laboratory monitoring usually detects DIN. In the outpatient setting however, symptoms such as malaise, anorexia, vomiting, shortness of breath, or edema may be the chief complaints. Fortunately, DIN is often reversible once the offending agents are discontinued.

Medications and DIN

The kidneys are highly susceptible to drug toxicity because of a large exposed vascular surface area, as they receive 20% to 25% of resting cardiac output. The kidneys are also susceptible because of the characteristics of renal physiology involved with blood flow regulation, intrarenal drug metabolism, urine concentration, and urine acidification. Advancing age, decreased renal blood flow, and inadequate hydration can increase the likelihood of DIN.

A number of different mechanisms underlie the pathogenesis of DIN, depending upon the inciting agent. For example, a number of drugs are recognized to cause damage to renal tubular epithelium. Aminoglycoside toxicity appears to be mediated by proximal tubular epithelial cell damage related to the cationic charge of the drugs. Radiocontrast-induced renal toxicity seems to be associated with direct tubular toxicity and renal ischemia. Platin-containing oncology drugs appear to bind to proximal tubular proteins and sulfhydryl groups, thus disrupting energy metabolism and uncoupling oxidative phosphorylation.[2,7,8]

Obstructive nephropathy can occur due to crystal precipitation within the tubules of the kidney. Drug-induced rhabdomyolysis from statin medications is one example, as is intratubular precipitation of sulfonamides or their metabolites.[9,10] Several drugs, such as lithium and cyclosporine, have been reported to cause chronic interstitial nephritis, which is usually progressive and irreversible. Further, more than 50 different medications such as NSAIDs and other pain relievers, neuropsychiatric medications, diuretics, and most classes of antibiotics including vancomycin have been implicated in causing allergic interstitial nephritis.[11-13]

Hemodynamic-mediated renal insufficiency results in a decrease in intraglomerular pressure. Mechanisms commonly include decreased renal blood flow, vasoconstriction of glomerular afferent arterioles, or vasodilation of glomerular efferent arterioles. For example, ACEI-mediated renal failure is attributed to decreased glomerular capillary hydrostatic pressure that is insufficient to maintain glomerular filtration usually due to reduced afferent arteriolar blood flow and efferent arteriolar vasodilation. NSAIDs can also induce renal failure within days of initiating therapy by blocking synthesis of vasodilatory prostaglandins. In situations where there is decreased renal flood flow, renal prostaglandins protect against renal ischemia and hypoxia by counteracting vasoconstriction mediated by norepinephrine, angiotensin II, endothelin, and vasopressin. However, administration of NSAIDs in the presence of decreased renal blood flow or renal ischemia can alter the balance between vasoconstrictors and vasodilators, leaving the vasoconstrictors unopposed, resulting in loss of glomerular filtration.[6]

DIN in Clinical Practice

In clinical practice, taking one medication associated with DIN may not create a problem for a given patient. However, in combination with other such medications, acute renal failure can develop quickly. For example, one common regimen characterized by co-administration of diuretics, ACEIs, and NSAIDs has been referred to as a “triple whammy” in the literature.[14] Diuretics reduce plasma volume, leading to reduced renal blood flow. This may result in a rise in serum creatinine. The kidneys compensate via the renin-angiotensin system by constricting the efferent renal arteriole to increase glomerular filtration pressure. However, the ACEIs inhibit efferent renal arteriolar vasoconstriction, which lowers glomerular filtration pressure. Furthermore, the NSAIDS lead to vasoconstriction of the afferent renal arteriole by inhibiting prostaglandin and bradykinin synthesis. Thus, when all three drugs are administered together, the kidneys are unable to engage normal compensatory mechanisms, and acute reductions in glomerular filtration can ensue.[15] In a large case-control study, this triple therapy was associated with a 31% increased risk of injury.[16]

Given the high incidence of DIN in both inpatient and outpatient settings, health professions learners should be able to recognize potential for this complication and propose medication dosing adjustments accordingly. Throughout the first 3 years of our medical school’s curriculum, the concepts of drug-induced renal injury, "triple whammy" medications, dosage adjustments, and basic pharmacokinetic concepts are discussed in a variety of settings that include lectures and both problem-based/team-based learning activities. Furthermore, students are provided with multiple laminated pocket cards to reinforce many of these concepts including basic pharmacokinetic equations. It should be noted that many of these educational modules have been previously published in MedEdPORTAL.[17-19]

To investigate learner aptitude with making connections between concepts spread across different courses and taught at disparate curricular times (e.g., basic science foundations, cardiopulmonary, renal, etc.) as well as the learner's ability to apply that information to actual patient care, a low-stakes, formative simulated assessment was developed. Simulation is a methodology that allows learners to apply their current mental model during an experience and provides opportunities to refine those mental models. The format also permits hands-on practice of skills while promoting competency and autonomy which are in-line with adult learning theories.[20] This standardized patient (SP) scenario is based upon an actual situation that involved a patient who had been previously admitted to the internal medicine service at our institution, was discharged, and returned to the emergency department several days later.

This scenario was implemented with third-year medical students but it could be easily extrapolated to other health care professional students with a background in pharmacology such as pharmacy, physician assistant, or nurse practitioner learners who will also be managing acute medication situations. During the encounter with the SP, students were expected to conduct a patient history and physical exam while maintaining professionalism and effective communication. During the note-writing portion of the case, students were specifically challenged to apply pharmacokinetic principles individualized to the patient's situation.

Methods

The case was developed primarily by Dr. Karpa, a pharmacist and pharmacologist, with additional input provided by internal medicine and family medicine physicians, a clinical pharmacist, and two fourth-year medical students. When developing this case, the authors were careful to develop a scenario that would encompass several different aspects of medication safety, such as identifying a patient problem as being medication-related and developing appropriate and thorough solutions. This case was designed as an internal assessment of our learners, and information gathered was used to inform the development of subsequent instructional activities. A prerequisite knowledge of pharmacology concepts is a necessity for successful completion of this activity.

Logistics

We implemented four medication-related SP cases at the same time, conducted over a 2-day period in a simulation center with all 23 of the third-year medical students at our regional campus. The simulation center rooms to which students were assigned did not have video capability, but each student-SP encounter was audio-recorded.

One time keeper is assigned to ensure that encounters are kept on time. With 15 minutes dedicated to the SP-student encounter, 1 minute allotted for walking to the computer for note-writing, 15 additional minutes to write the note, 3 minutes for the SP to provide feedback, and 1 minute to rotate to the next station (of four different medication-related cases), in total 35 minutes is allotted for each student to complete this scenario. A master schedule for time keeper verbal instructions (Appendix H) identifies minute-by-minute actions of the students. The overall flow of the day, demonstrating how each student progresses through the cases, is outlined by the student schedule (Appendix G). The SP scenario presented in this module is the third case (Case 3) in the sequence.

Over the course of a day, the SP enacting this case encounters four students in the morning, four in an early afternoon session, and four in a late afternoon session. Although the SP has to arrive early for the application of moulage, the acting portion of the SP's day begins at 9:00 AM and finishes at approximately 5:45 PM, with a 1 hour lunch break. To reproduce this SP experience, Appendix A describes logistical information for the SP in greater detail, Appendix B includes materials for training the SP, Appendix C describes recruitment materials, and Appendix D contains behavioral measures as well as time keeper materials.

This particular scenario is set in a primary care office setting. The students are provided with student instructions (Appendix F) for part one and part two of the case. Part one instructions provide students with a general overview of the patient they are about to encounter, including vital signs. Students are asked to gather necessary information from the SP, assess the SP's problem, and then effectively communicate a plan to the SP before leaving the room. Students are given 15 minutes to accomplish this. Part two instructions inform students they would be writing a note using the subjective, objective, assessment, plan (SOAP) format and answering very specific questions. They are asked to include positive and negative findings from the history and physical in the development of their differential diagnosis. They are also asked to apply pharmacokinetic knowledge in making appropriate dosage adjustments. Students have 15 minutes to write their note and submit it electronically.

SP Training Materials
Examples of materials that can be used to advertise and recruit SPs are included as Appendices J and K. The specific materials that we utilized to train the SPs are included in Appendix E. Training materials are provided to the SPs 2 weeks in advance so that they can review the material prior to formalized training with a faculty member. Included within this document is an SP checklist for student assessment, which was used by the SP to indicate what the students had asked about, what skills the student had performed, and what information the student provided to the SP about the current situation. The SP is asked to complete the checklist immediately after each student exits the room while the student write his/her SOAP notes. After SOAP note completion, students re-enter the SP room for 3 additional minutes to allow the SP to provide feedback to the student.

Preparation and SP training
Two individuals may be trained as SPs for this case. One SP is trained as the primary SP. The other is trained as a backup in case the primary SP had a conflict or illness on event dates. In our experience, the primary SP was the only SP used for all 23 students who participated in the scenario. This SP had previously worked as a dental hygienist before retirement and she had a working knowledge of the health care system as well as experience in health care education-related settings, and was able to provide feedback. In this case, since the trainer was also the creator of the case, changes were made to the case when the SP had appropriate ideas to incorporate.

During training, a faculty member reads the case aloud with the SPs, communicates the rationale behind specific case components, and answers any questions that the SPs have. In addition, the SPs and the faculty member also engage in role-playing. The SP who was not role-playing is able to observe and critique. During training, SPs complete the checklist which is reviewed and discussed among the SP trainees and faculty member for accuracy. If there were any checklist items that are unclear, these are reviewed and corrected at the time of role-play.

The SPs are given instructions for providing feedback to students. To provide context for the types of feedback they would be providing to learners, SPs were asked to reflect on ways they or family members felt when treated by various health care professionals in past authentic encounters. Discussions included statements such as "I feel like my doctor listens to me when . . . ," "I felt disrespected when . . . ," "I feel scared when . . . ," "I feel like the doctor may not know what to do about my condition when . . . ," and so forth. When providing feedback with students, the SP is instructed to first ask the students to reflect on their performance during the encounter. This is followed by the SP providing general thoughts about the encounter that focused upon how the student made the SP feel as a patient (e.g., confident, comfortable, worried, scared) as well as the behaviors or mannerisms of the student that prompted these feelings. The SP then asks the students to reflect on what they will do differently the next time they encounter a similar situation in patient care.

Faculty Involvement

A single faculty member listens to all audio recordings of each scenario. Some discrepancies between the SP's recall and the audio may be noted. Specifically, in our experience we found that sometimes the SP volunteered information relevant to the case without waiting for students to make a specific inquiry. Yet, in these instances, the SP identified on the checklist that the student had completed the task. Thus, the audio is used as the definitive record to confirm if the student, as opposed to the SP, had completed the task or made the inquiry. Faculty assess SOAP notes according to the Faculty Assessment Materials document (Appendix I).

Results

To date, this scenario has been used with all 23 third-year medical students at our regional campus. Table 1 demonstrates data gathered from SP-student interactions. Table 2 demonstrates data gathered from written student SOAP notes.

Table 1. Summary From SP Checklist[a]

	% Correct	
Item	**Assessed by SP**	**Assessed by Faculty**
History	82	61
Physical examination	68	Not assessed
Assessment	59	32

Abbreviation: SP, standardized patient.
[a]Appendix E.

Table 2. Summary From Student SOAP Notes

Item[a]	**% Correct**
Subjective	47.8
Objective	27.5
Assessment	65.2
Plan	2.2

Abbreviation: SOAP, subjective, objective, assessment, plan.
[a]As rated by faculty using Appendix I.

The SP's recall of events appeared to be more generous than the score provided by faculty when listening to the audio. When individual items on the checklist were examined in greater detail, nearly all students asked when symptoms began (19 of 22) and what medications the patient was taking (19 of 22). On the other hand, only three students asked about urinary symptoms. Since only audio recordings were available, faculty were unable to verify physical exam skills. Yet, based upon the SP's checklist, nearly all students (22 of 23) examined the original site of infection and most (21 of 23) examined the SP's ankles. However only 8 of 23 students palpated the SP's lower back and only three students checked the patient's pedal pulses. At the end of the encounter, only seven students communicated to the patient that the symptoms were in any way attributed to a drug reaction with the kidneys, per faculty review of the audio. Specifically, it was hoped that students' assessment of the SP would include drug-induced kidney problems; but, if SP merely heard the words "drugs" or "kidneys," the SP awarded students credit, thus accounting for the discrepancy between the SP and faculty member. Even with the faculty member scoring generously on this item, it was unclear if students correctly ascertained which drugs (e.g., the lisinopril-ibuprofen-hydrochlorothiazide combination) had elicited the problem. Students were quite vague in their assessment of the situation when they attempted to provide the SP with an explanation for her symptoms. Several students incorrectly concluded that the patient was having heart problems, a urinary-tract infection, or a persistent cellulitis infection. Rather than recognizing elevated plasma vancomycin levels as a side effect of acute renal failure induced by a common triple drug combination, almost half of the students incorrectly conveyed to the patient that her problems were directly attributed to a reaction to her antibiotic, thus failing to notice that the SP had been fine until returning home. Students neglected to explore and synthesize the ways in which the SP's situation at home differed from that of her prior admission.

When SOAP notes were assessed, students were most likely to score points for identifying pertinent positive and negative criteria to support a differential diagnosis as they completed their assessment of the situation. After having an opportunity to utilize resources, eight students identified renal problems due to ibuprofen and/or blood pressure medications. Despite this, students often failed to develop an appropriate plan for the patient. Only 2 of 23 students suggested the patient discontinue use of ibuprofen. None of the students recommended the SP temporarily discontinue/hold use of the lisinopril, and only one student suggested the SP hold the use of the diuretic hydrochlorothiazide. Most students were able to recognize that vancomycin is renally eliminated; however, none successfully applied pharmacokinetic dosing principles to appropriately account for the patient's recent decline in kidney function, and correctly answer the specific question raised in part two of the case.

Discussion

Since it is known that students had previously been exposed to all the concepts on which this scenario is based, it is a bit discouraging that the students did not perform better on this exercise. Yet previous work from others indicates that using knowledge acquired in one context to solve a new dissimilar problem in another context, also known as knowledge transfer, is far more difficult than anticipated. Students who have learned a concept in one setting have only a 10% to 30% success rate when applying that concept to a new problem.[21] Furthermore, it is unlikely that students spent time preparing or reviewing pharmacologic concepts specifically for the medication OSCEs since we were unable to link the exercise to one specific clerkship and assign a grade as students were spread across 10 different clerkships at the time this activity was performed. Since assessment drives learning, it is possible that a different outcome would have been achieved if we had implemented this medication scenario as a high-stakes examination. An additional limitation to the way that we implemented this activity may stem from the fact we did not provide immediate debriefing for the learners. Our learners are not normally debriefed in detail after OSCEs, so this is not unusual at our institution. However, there may be advantages to providing immediate feedback to learners about concepts with which they are unfamiliar.

Interestingly, even though not a single student found the patient's specific clearance of vancomycin or found the corresponding half-life given the patient-specific clearance, we did gain insight into students' thought processes about the application of simple pharmacokinetics by reading their SOAP notes. Some students recalled that it takes four or five half-lives to effectively eliminate a drug; therefore, they looked up the published half-life of vancomycin in healthy patients, and used that parameter in their calculation. Unfortunately, these published values only work for otherwise healthy individuals and did not apply in this situation due to the SP's compromised renal function. Another student response to the pharmacokinetic question was to "call a pharmacist." With this thought in mind, it may be interesting to explore implementing this scenario as an interprofessional team simulation case in which pharmacy learners can contribute their discipline-specific knowledge. This may be applicable to institutions that have both medical and pharmacy schools. However, on the other hand, pharmacy students have year-long courses devoted to pharmacokinetic applications, whereas medical students may be exposed to as little as an hour of basic, introductory pharmacokinetic applications. Therefore, the equations that are taught to the medical students to estimate pharmacokinetic parameters, are nowhere as precise as the formulas used by pharmacy students. Thus, this disconnect may present a source of frustration between the learners.

As more medical schools opt to delay having their learners complete the USMLE Step 1 exams until after the third year of medical school, it will become increasingly important that learners be able to tie basic science concepts with clinical application. Indeed, vertical integration of basic sciences with clinical medicine has been implemented at many institutions as part of medical education reforms in recent years.[22] Over the past several years, a medication prescribing skills assessment has been implemented in the UK as an examination that must be passed by fourth-year medical students prior to graduation. This examination was implemented as a means for soon-to-be graduates to demonstrate competence in safe and effective prescribing skills.[23] Perhaps with the recent trend towards competency-based medical education, it is time to consider implementing a similar assessment in the United States as well. To this end, our university offers, and medical students are enrolled in a patient-centered medical home elective learn to apply basic science pharmacology concepts in a patient care setting by practicing medication reconciliation with their own population of patients. In the beginning of the course, as measured by a baseline assessment, they are only able to identify an average of 33% of medication-related problems in a standardized patient case. Many of those problems involve pharmacokinetic and pharmacodynamic concepts of metabolism, elimination, pharmacokinetics, and interactions. However, by the end of the longitudinal course, after immersing themselves in the habit of revisiting basic science pharmacology concepts in clinical care, they are able to identify nearly twice as many problems (58%), suggesting that vertical integration of basic science concepts to patient care has the potential to improve patient outcomes.[24]

Overall, this endeavor highlighted the need for students to revisit and apply concepts that were learned in the context of basic science to clinical care. Since drug-induced nephropathy is a common condition, students must learn to consider it as a possibility, learn which drugs are renally eliminated and require dose adjustments for changes in kidney function, and know how to apply pharmacokinetic properties. As a result, we have used the information provided by this exercise to add medication safety concepts and pharmacokinetics to a third-year course that focuses on revisiting basic science concepts in clinical care

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