

Correct diagnosis, wrong medication, unusual adverse event

Abstract

Case study: A 37 year old woman with a history of migraines presented to an urgent care center with an atypical headache. She had awakened with the headache, an uncommon occurrence for her. Although severe, the headache was different in character compared with her usual migraine headaches and was unrelieved by her usual migraine medication. Careful investigation revealed that she had used permethrin, applying it her skin from neck to feet prior to going to bed the previous night. The patient had consulted a family nurse practitioner (FNP), at her place of employment, for an “ugly” rash. The FNP had correctly diagnosed the rash as *astineacporis* but prescribed treatment indicated for scabies. The patient’s headache was successfully treated with Toradol and intravenous fluid bolus.

Permethrin: Permethrin is a neurotoxin, used extensively as a pesticide and insect repellent. It is classified as a restricted use pesticide (RUP) by the Environmental Protection Agency (EPA) due to its toxic effects on aquatic life and beneficial insects, such as honey bees.¹ Although little is known about its neurotoxicity in humans,² permethrin is first line treatment for scabies, considered safe for infants as young as two months old.³ Systemic adverse events are reportedly rare, but do include headache.⁴

Discussion: Adverse drug events (ADEs) resulting from errors, considered preventable ADEs, are associated with unacceptable costs to the US healthcare system, in addition to inordinate pain and suffering.⁵ A preventable (ADE) resulting from the wrong medication being prescribed for a correctly diagnosed condition could potentially be avoided by the inclusion of a diagnoses on medication prescriptions. Error checks built into software systems could alert practitioners and/or pharmacists of a mismatch between medication and indication. Further research is needed to investigate the feasibility and value of potential interventions for reducing preventable ADEs.

Keywords: correct diagnosis, wrong medication, unusual adverse event

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Abbreviations: FNP, family nurse practitioner; RUP, restricted use pesticide; EPA, environmental protection agency; ADE, adverse drug event; WHO, world health organization; IOM, institute of medicine

Case study

A 37 year old white woman with a well-known history of migraine headaches presented to an urgent care center with a chief complaint of severe headache with associated nausea that was unrelieved by medication that she had at home. She had taken Axert® (almotriptan) at home and repeated it once, without any improvement in her symptoms; she typically had good results with this medication. Upon presentation to the urgent care center, she had been given Zofran 4 mg disintegrating tablet with minimal improvement in her nausea. She rated the pain of her headache as eight (8) on a scale of 1-10. The patient reported awakening with the headache on the morning of presentation. She reported pain “all over” her head, which began in the frontal region; she admitted that this was not typical of her migraine headaches which usually began unilaterally in her temple area. In spite of the almotriptan, her headache worsened while she was taking a shower. When another dose of almotriptan failed to provide any relief, she was brought into the urgent care by her husband.

When the patient was asked about the events of the previous day,

she initially could not identify anything different than usual. She reported having had an uneventful day at work followed by a quiet evening at home with her husband and son. Upon further questioning, she recalled that because she was not having a busy day at work, she had decided to take advantage of a new benefit provided by her employer. The employer had recently hired a family nurse practitioner (FNP) to provide healthcare services for employees on-site. This type of healthcare benefit is becoming more popular among employers in an effort to cut costs with insurers. The patient said that she had had a rash for several months and that she had been thinking about consulting the FNP about it. She denied that the rash had worsened or changed recently. She admitted that it was itchy at times, but this was not different. When asked why she wanted to get rid of it, she stated because it is “ugly”. She denied any reason other than convenience for seeking treatment for the rash at this time.

The patient reported that the FNP diagnosed her rash as “fungus” and prescribed a lotion. The patient reportedly applied the lotion to her entire skin from her neck to her feet prior to going to bed the previous evening and washed it off in the morning, as per the instructions. She denied being concerned about the treatment and denied any problems or concerns regarding the application of the lotion. She reported having slept well. Upon awakening with a headache, she took almotriptan. She then took a shower as per her normal morning routine. To her dismay, her headache continued to worsen and was not

relieved with an additional dose of almotriptan. She stated that this was the first time this medication had failed to relieve a headache for her. By the time she presented to the Urgent Care Center, having used the cream the night before had initially slipped her mind.

On examination, the patient appeared very uncomfortable; she had tears in her eyes. She was lying on the exam table covered with a blanket in a darkened exam room. Her apparently concerned husband was standing by her side. Her physical examination, including a thorough neurological exam, was completely normal, except for her skin. She had a few oval shaped, well demarcated, tan colored, slightly scaly lesions, approximately 1-2 centimeters in size, scattered on her lower trunk and upper thighs. She indicated that this was the rash for which she had consulted the FNP and used the prescription lotion. She expressed disappointment that it was still present, having thought that the treatment would eliminate it immediately. Her skin was otherwise without rashes or lesions, in particular, there were no papules, blisters, nor burrows. The skin of her hands, feet and genital region was clear. Neither the patient nor her husband could remember the name of the prescription lotion that the patient had used the previous evening. A telephone call to the pharmacy revealed that it was a prescription was for Elimite™ (permethrin). Permethrin is a neurotoxic and headaches have been reported as a rarely occurring adverse event with therapeutic doses. Severe headache is a classic symptom of overdose. The temporal relationship between the use of permethrin and the occurrence of the headache makes the permethrin suspect. This suspicion is supported by the atypical nature of the headache and an inability to identify any other potential precipitators associated with the headache.

Establishment of a direct and cause and effect relationship between the headache and permethrin could only be accomplished by a re challenge of the patient with the medication. This was not a reasonable option in this case, especially given that the medication was

not indicated for this patient's rash (i.e. it was incorrectly prescribed); the risk would unwarranted given no potential benefit. The temporal relationship between the drug and the adverse event and the lack of any compelling alternatives explanations for this atypical headache constitutes a reasonable possibility that the permethrin caused the headache.¹ no compelling alternative explanations.

The patient was educated about the probable relationship between permethrin and her headache, as well as the indications for permethrin and medications indicated for the treatment of fungal infections of the skin. She expressed some concern that she may not have washed the lotion off as thoroughly as she should have. She was treated with Toradol (ketorolac) 60mg intramuscularly with some relief; pain level decreased to six (6) on a scale of 1-10. After an intravenous fluid bolus of one liter normal saline, the headache and nausea were almost completely resolved. She was instructed to thoroughly bathe again as soon as she got home and to drink plenty of fluids. It was recommended that she follow up with her primary care provider or a dermatologist for further evaluation and treatment of her skin rash.

Permethrin

Permethrin is available over the counter in a 1% preparation and by prescription in 5% topical cream, indicated for treatment of head lice (*Pediculushumanuscapitis*)⁶ and scabies (*Sarcoptes scabies*)⁷, respectively. Permethrin (Elimite™) 5% is first line treatment for scabies, reportedly safe for patients two months of age and older.³ Permethrin 5% is sold under at least fifty different brand names (Table 1). The most common adverse event is pruritis, reported in up to 7% of patients. Other common side effects, reported in 1% to 2% or fewer patients, include erythema, numbness, tingling and rash. There have been post-marketing reports of headache, fever, dizziness, abdominal pain, diarrhea and nausea and/or vomiting. Rare occurrences of seizure have been also been reported.⁴

Table 1 Brand names for permethrin 5%

Brand Name	Manufacturer	Brand Name	Manufacturer
Acticin	Bertek Pharmaceuticals Inc.	Permicer	Avancer Labs (P) Ltd
Alpermy	Densa Pharmaceuticals	Permiriv Lotion	East African (I) Remedies (P) Ltd
Clearkin	Ind-Swift Limited	Permiskin	Biochemix Healthcare Pvt Ltd
DAT	Omega Remedies Pvt Ltd.	Permiskin Cream	Micro Labs Ltd (Gratia)
Elice	Zee Laboratories Ltd	Permisol	CaptabBiotec
Elimite	Prestium Pharma, Inc.	Permite	Galderma India Pvt. Ltd
GzIthrin	Gedzrlvin Pharmaceuticals	Permizo Cream	Zodley Pharmaceuticals Pvt Ltd
Jolice	Cure Quick Remedies	Permizo	InvisionMedi Sciences
Lyscab	Lyra Laboratories Pvt Ltd	Persure	Sunways India Pvt. Ltd
Medilice	Wings Pharmaceuticals	Pertel	Intel Pharmaceuticals
Mityscab	Fem Care Pharma Limited	Pertop	Dermocare Laboratories (Guj) Pvt Ltd
Monoscab	Geolife Sciences	Scabenil	Psychotropics India Limited
Monoscab Cream	CaptabBiotec	Scaberase	Rowan Bioceuticals (P) Ltd
Nomite	Apids Pharmaceuticals	Scabex P	Indoco Remedies Ltd (Spera)
Noscab	Psyco Remedies.	Scabicide	Mercury Laboratories Ltd
Parmath	Ecliper Pharmaceuticals	Scaboz	Daksh (Zodak Pharmaceuticals)
Pedicor	Grace Drugs Pharmaceuticals	Scabper	Shalaks Pharmaceuticals Pvt. Ltd

Table Continued..

Brand Name	Manufacturer	Brand Name	Manufacturer
Pedimite	Neiss Labs Pvt. Ltd.	Scadis	Medis Lab
Peloscab	Elfin Pharma Pvt Ltd (Biotropics Form.)	Scalix	Zee Laboratories Ltd
Peloscab Cream	Gujarat Terce Laboratories Ltd.	Scanil	Zodley Pharmaceuticals Pvt Ltd
Perclin	Affy Pharma Pvt. Ltd	Scatik	Axyzen Life Sciences
Perin	Novasearch Dermocare	Skabiz	Archicare
Perlut	Canbro Healthcare	Skabkill	Unichem Laboratories Ltd
Permarid	Micro Labs Ltd (Gratia)	Uniscab	Gujarat Terce Laboratories Ltd
Permarid Cream	InvisionMedi Sciences	Viscab	Arlak Biotech Pvt Ltd
Permethrin Cream	Renaissance Pharma, Inc.		

Permethrin is widely used as an agricultural and industrial pesticide and as an insect repellent in mosquito nets and military uniforms. Permethrin is a neurotoxin which kills lice, ticks, fleas, mites and other arthropods through paralysis. The US Environmental Protection Agency (EPA) classifies it as a restricted use pesticide (RUP)¹ due to its high toxicity to fish and other aquatic organisms.⁸ Its use in agriculture is also controversial because it is harmful to beneficial insects such as honey bees.⁹ Permethrin reportedly has low mammalian toxicity, but its use in flea collars revealed that it is dangerously toxic to cats, inducing hyperexcitability, tremors, seizures and even death.¹⁰ Medical use of permethrin is extensive. It is on the World Health Organization's (WHO) of essential medications needed in a basic healthcare system.¹¹ In spite of its widespread use for decades, there is limited data on the neurotoxicity of permethrin in humans.²

Discussion

A causal relationship between the use of a specific drug and an adverse event is often difficult to establish. In this case, the temporal relationship of exposure to permethrin and presentation of an atypical headache in a migraine sufferer is suspect. Permethrin is reportedly well tolerated, poorly absorbed through skin and rapidly metabolized in humans.¹² Reports of systemic effects have been uncommon.¹³ It is important to consider that adverse effects are likely to be underreported for a medication such as permethrin, which is most often prescribed in walk-in clinic settings where follow up is unusual. In addition, patients are less likely to complain about side effects of a medication for which repeat use is unlikely. Headaches are common occurrences and a temporal relationship with the use of permethrin could easily be disregarded, as it was by the patient in this case.

The patient's skin lesions were consistent with tineacorporis, a superficial skin infection caused by fungus. The usual treatment for tinea is application of a topical antifungal once or twice daily. Treatment is typically recommended for at least three weeks.¹⁴ The method of treatment described by the patient was consistent with treatment for scabies and verification of the medication prescribed confirmed it was indicated for scabies. Scabies, also known as "the seven year itch", is a condition of very itchy skin caused by tiny mites that burrow into the superficial layer of skin. The rash of scabies consists of papules, vesicles and burrows most commonly seen on the webbing between the fingers and/or toes, wrists, elbows, waist and genital region.¹⁵ It appeared that the patient's skin condition had been diagnosed correctly, but that the medication prescribed was not indicated for her condition.

This case illustrates the importance of careful prescription

practices. There are risks involved with any medication and adverse drug events (ADEs) will inevitably occur. It is imperative to carefully weigh the potential benefit and risk of any medication prior to writing a prescription. Ideally, this should be discussed with the patient to ensure potential benefit outweighs potential risk for the individual patient. ADEs that result from prescription errors are considered preventable ADEs.¹⁶ The Institute of Medicine (IOM) estimated that at least 1.5million preventable ADEs occur in the United States each year, but acknowledges that this is very difficult to measure and the actual number may be much higher.⁵ There are no reliable estimates of the costs of preventable ADEs to the US health system.¹⁷ In addition to financial costs, preventable ADEs result in significant pain, suffering and sometimes even death. With the rapidly increasing use of medications in the US, reducing risk of preventable ADEs is a critical patient safety and public health challenge.

Reducing the risk for preventable ADEs is complex and will require a concerted effort by healthcare providers, pharmacists, regulators, information technicians, as well as patients. Improving education and communication and increased use of technology have been identified as key prevention strategies.¹⁷ Cases in which the wrong medication is prescribed for a correctly diagnosed condition could potentially be prevented by the diagnosis being included on the prescription. Hopefully, an astute pharmacist would notice the inconsistency between the diagnosis and prescribed medication; make a call to the practitioner and avert the problem. In addition, checks could be built into software systems for inconsistencies between a diagnosis and a prescription medication, prompting an alert to the prescriber and/or pharmacist. Research is needed to determine the incidence of this particular type of preventable ADEs and the feasibility and value of possible interventions.

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None.

Conflict of interest

The author declares no conflict of interest.

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