

# Potential therapeutic hazards due to drug–drug interaction between topically and systemically coadministered medications

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## Dear editor

We read with great interest the study by Peniston et al<sup>1</sup> who performed a randomized controlled trial to examine the frequency and type of adverse events (AEs) in patients with osteoarthritis who received concurrent therapy of topical diclofenac sodium 1% gel (DSG), and drugs known to have potential drug–drug interactions (DDIs) with diclofenac; and concluded that such co-medication had little impact on the frequency of AEs in this population.

The results of this study<sup>1</sup> provide very useful information for clinical practice, ie, DSG may be a safe alternative to oral diclofenac when a pain reliever needs to be co-medicated with CYP2C9 substrates like warfarin antidiabetic sulfonylurea derivatives. DDIs between topically and systemically coadministered medications are easily neglected by clinicians, which brings about potential risk of patient safety. Peniston et al<sup>1</sup> answered a scientific question in clinical therapeutics. We completely appreciate their rigorous study and original spirit of exploration. We would like to discuss and share our perspectives in the following paragraphs.

The Joint Commission International (JCI) accreditation standard has strict requirements for rational drug use. Appropriateness review of real or potential DDIs among all current medications is a mandatory task for auditing pharmacists.<sup>2</sup> Peniston et al's study further prompted us to better understand JCI requirements. We performed a PubMed search covering the period from 1988 to 21 June 2013, using the search terms “topical” and “drug interaction” and additional filters (species: humans; languages: English). Nine hundred and twenty-eight articles were detected. Inclusion criteria included studies or case reports describing DDIs between topically and systemically coadministered medications even if results of some clinical trials show no clinical significance. Fifteen articles were finally included under this search strategy. The full text of each article was critically reviewed, and data interpretation was performed. Table 1 lists the literature describing DDIs between topically and systemically coadministered medications, except Peniston et al's study.

For each DDI, the object drug is defined as the medication whose pharmacokinetics and/or pharmacodynamics may be modified by the drug interaction process. The precipitant drug is defined as the medication responsible for affecting the pharmacologic action or the pharmacokinetic properties of the object drug.<sup>16</sup> Our literature review showed an interesting fact that topically administered medications could play a role of object drug in addition to a role of precipitant.

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**Table 1** Drug–drug interactions (DDI) between topically and systemically coadministered medications

Topically administered medications	Systemically administered medications	DDI information	Clinical management
<b>Co-medicated as an object drug</b>			
Topical dapsone gel	Oral trimethoprim/sulfamethoxazole (TMP-SMZ)	Dapsone prescribing information shows that coadministration of oral dapsone and oral trimethoprim increase the plasma concentrations of each agent approximately 1.5 times compared with monotherapy. However, co-medicated dapsone gel (applied twice daily for 14 days to 22.5% of the body surface area) has no significant effects on pharmacokinetics of either trimethoprim or sulfamethoxazole. Total systemic exposure to dapsone was approximately 100-fold less for dapsone gel than for oral dapsone, even in the presence of TMP-SMZ. None of hematological adverse events was observed. DDI between topical dapsone and oral TMP-SMZ is not clinically meaningful. <sup>3</sup> A elderly patient with glaucoma experienced dizziness and sinus bradycardia induced by DDI between oral quinidine and timolol eye drops. <sup>4</sup> The potential mechanism is that timolol maleate can be absorbed from the conjunctiva and nasal mucosa with a bioavailability approximately 50% of that after oral administration, and quinidine can impair CYP2D6-mediated timolol metabolism. A randomized clinical trial shows that the effects of topically administered timolol are dependent on the individual CYP2D6 phenotype and co-medicated oral quinidine can inhibit metabolism of timolol and increased beta-blockade. Furthermore, administration of quinidine with timolol eye drops to extensive metabolizers (EMs) resulted in a further significant reduction in heart rate ( $P = 0.02$ ) and increase in plasma timolol concentration ( $P = 0.04$ ) compared with poor metabolizers (PMs). <sup>5</sup>	Topical dapsone gel is an alternative formulation for the treatment of acne vulgaris, with the advantages including greatly minimizing the systemic exposure to dapsone, avoiding the adverse hematological effects and DDI potential observed with oral dapsone therapy.
Topical timolol maleate	Quinidine		<ol style="list-style-type: none"> <li>1. Patients are often advised to compress the nasolacrimal duct during and after application, in the belief that this may reduce systemic absorption.</li> <li>2. If adverse effects are still encountered or anticipated, use of an agent with minimal systemic absorption like metipranolol eye drops, can be considered.</li> <li>3. Clinicians should be aware of the potential for drug interactions that occur when orally administered drugs inhibit the metabolism of a topically administered drug.</li> </ol>
<b>Co-medicated as a precipitant drug</b>			
Nystatin solution	Warfarin	After use of topical nystatin, the mean international normalized ratio (INR) in eight patients increased from 2.5 to 10.6 ( $P = 0.0001$ ) and the mean weekly warfarin dose had to be decreased from 14.5 mg to 9 mg ( $P = 0.038$ ). <sup>6</sup>	If topical nystatin is required by patients already on warfarin, warfarin dose down to half the established dose and close monitoring of INR (eg, 3–5 days after introducing the antimycotics) may be required.
Econazole cream	Warfarin	A 79-year-old patient on warfarin experienced significant increase in INR from 2.2 to 12 after coadministration of econazole cream (applied twice a day for one week). After immediate discontinuation of econazole and treatment with 5 mg of oral vitamin K, the INR fell to within acceptable limits within 5 days. <sup>7</sup>	Patients taking warfarin should be advised to avoid topical treatment with econazole or miconazole. If this is not possible, control of anticoagulation must be monitored closely.
Miconazole cream	Warfarin	Devaraj et al reported a case of over anticoagulation in an 80 year old patient taking miconazole cream for flexural intertrigo. After two week topical treatment, the patient's INR dramatically jumped from 2.2–3.1 to 21.4. <sup>8</sup> The possible mechanism for this drug interaction may refer to topically absorbed miconazole inhibits CYP2C9-mediated warfarin metabolism.	

Topical terbinafine	Acenocoumarol	<p>After 15 days of topical terbinafine (1% spray solution) treatment once daily for seborrheic dermatitis, the INR values of 71-year-old patient on acenocoumarol and diltiazem were greater than 8, whereas INR values over the past year had been between 2.0 and 3.0. Mechanisms for possible interaction might involve displacement of acenocoumarol from plasma protein-binding sites by addition of topical terbinafine and indirect inhibition of acenocoumarol drug metabolism (ie, terbinafine impaired CYP2D6-mediated drug metabolism of diltiazem and elevated diltiazem level increased the magnitude of CYP3A4-mediated metabolism inhibition toward acenocoumarol).<sup>9</sup></p> <p>A 84-year-old patient on acenocoumarol experienced over-anticoagulation and a life-threatening laryngeal hematoma after the addition of topical econazole lotion for 1 month. The episode was probably related to an interaction between acenocoumarol and econazole.<sup>10</sup> Systemic absorption of topical econazole in healthy subjects was &lt;2%, however, it may be increased by application to a large area of the body surface, application under occlusion, or application to thin, macerated, or ulcerated skin, which may result in enough systemic concentrations and metabolic inhibition of CYP system.</p>
Topical econazole lotion	Acenocoumarol	<p>A study of eleven patients on warfarin showed that all patients had abnormally elevated INR values and six patients exhibited side effects (eg, bleeding manifestation, bruises and gastrointestinal bleeding) after significant usage of topical methyl salicylate ointment.<sup>11</sup> A female patient on warfarin had an INR of 12.2 after applying topical methyl salicylate gel to her knees daily for 8 days.<sup>12</sup> Topical methyl salicylate can be systemically absorbed and may increase warfarin action by affecting vitamin K metabolism or by displacing warfarin from protein-binding sites.</p>
Topical methyl salicylate	Warfarin	<p>A randomized, open-label, 5-way crossover study was conducted to evaluate the pharmacokinetic/pharmacodynamic interaction between furosemide and the non-steroidal anti-inflammatory drugs diclofenac and ibuprofen in healthy volunteers. Diclofenac topical patch (1.3% applied topically twice daily) had no pharmacokinetic or pharmacodynamic effects on intravenous furosemide. However, coadministration of oral diclofenac (75 mg taken orally twice daily) decreased maximal sodium and potassium excretion rates and urine output by about 9%–15% and co-medicated ibuprofen (800 mg taken orally thrice daily) delayed furosemide elimination.<sup>13</sup></p>
Diclofenac epolamine topical patch	Intravenous furosemide	<p>On April 8, 2009, the database of The Netherlands Pharmacovigilance Centrum Lareb contained five reports about an interaction between topical imidazole derivative with statin, including a case of rhabdomyolysis (CK &gt; 8000) and a case of tiredness and muscle weakness due to concomitant use of ketoconazole cream and atorvastatin 20 mg, a case of myalgia due to concomitant use of miconazole cream and simvastatin 20 mg, two cases of myalgia due to coadministration of ketoconazole cream and simvastatin 20 mg or 40 mg. The time to onset of the adverse drug reaction of the statin varied from one day to two weeks. Patients of four cases recovered after discontinuation of topical miconazole or ketoconazole. The absorption of the imidazole derivative could have been influenced by application on a large surface in one patient and under occlusion by using the cream in the armpits in two patients.<sup>14</sup></p>
Ketoconazole cream Miconazole cream	Stains	<p>To avoid renal complications, health care providers may select diclofenac epolamine topical patch instead of oral nonsteroidal anti-inflammatory drugs for patients taking loop diuretics.</p>
		<p>Health care providers, and patients taking simvastatin or atorvastatin must be aware of the potential hazard of concurrent therapy of topical miconazole or ketoconazole and excessive usage of the two topical medications is to be avoided.</p>
		<p>Health care practitioners should inform patients about the potential interaction between acenocoumarol and econazole, and educate them to recognize the signs and symptoms of bleeding. Close monitoring of the INR, and appropriate adjustment of the coumarin dose may be advisable to avoid over-anticoagulation and the risk of bleeding.</p> <p>Health care providers and patients taking warfarin must be aware of the potential hazard of using topical methyl salicylate in combination with warfarin and excessive usage is to be avoided.</p>

(Continued)

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Topically administered medications	Systemically administered medications	DDI information	Clinical management
Topical rifamycin SV	Cyclosporin	A decrease in blood cyclosporin level from 160 ng/mL to 100 ng/mL was observed in a renal graft recipient receiving maintenance immunosuppression therapy with cyclosporin 5 mg/kg and prednisone 10 mg per day during surgical wound irrigation with topical rifamycin SV solution (500 mg in 1000 mL physiological saline solution, three times a day). The trough cyclosporin levels increased immediately after withdrawal of topical rifamycin SV, suggesting that the interaction between rifamycin SV and cyclosporin might be associated with changes in the bioavailability or elimination of cyclosporin. <sup>15</sup>	Whatever the mechanism, the possible interaction should be considered by physicians and surgeons, who often use the antibiotic topically. In renal transplant recipients receiving cyclosporin who require local rifamycin SV solution, the blood cyclosporin level should be closely monitored.

Some factors may influence the likelihood of DDI between topically and systemically administered medications and they are as follows: (1) percentage of body surface area to which the topical formulation is applied; (2) age of the patient – the very old and very young are more likely to exhibit DDI; (3) genetic factors may affect the magnitude of DDI (eg, DDI between timolol eye drops and oral quinidine is dependent on CYP2D6 phenotype; poor metabolizers have a higher risk for DDIs with a low systemic concentration of a topical imidazole derivative than extensive metabolizers do);<sup>5,17</sup> (4) method of application—medications applied under occlusion are more likely to cause DDI; (5) condition of the stratum corneum—topical formulations applied to mucous membranes, genital skin, or thin, macerated, or ulcerated skin are more susceptible to be systemically absorbed; and (6) other concomitantly used medications are also involved in the DDI mechanism, eg, topical terbinafine (precipitant drug) impaired CYP2D6-mediated drug metabolism of diltiazem and elevated diltiazem level increased the magnitude of CYP3A4-mediated metabolism inhibition toward acenocoumarol (object drug).<sup>9</sup>

Methods used for judging whether there are DDIs between topically and systemically administered medications are as follows: (1) pharmacokinetic interaction study; (2) randomized controlled clinical trials focusing on overall tolerability of topical formulation with concomitant use of systemically administered medication; and (3) case analysis by using the Horn Drug Interaction Probability Scale or Naranjo scale.<sup>9,10,18</sup>

In conclusion, Peniston et al's<sup>1</sup> study brought an interesting and important topic to clinicians and patients who should be careful of potential therapeutic hazards due to DDIs between topically and systemically coadministered medications.

## Acknowledgment

This work was supported by Zhejiang Provincial Bureau of Health (No 2012KYA090), and Zhejiang Provincial Bureau of Traditional Chinese Medicine (No 2011ZB075).

## Disclosure

The authors report no conflicts of interest in this work.

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