Possible Interaction Between Topical Terbinafine and Acenocoumarol

TO THE EDITOR: Terbinafine, an allylamine derivative, is an antifungal agent that inhibits ergosterol synthesis, destroying the fungal cellular membrane. Acenocoumarol, an anticoagulant agent, has a vitamin K antagonistic effect. Both drugs present high affinity to plasma proteins and are metabolized by cytochrome P450 isoenzymes. In addition, topical terbinafine formulations might present systemic absorption (less than 5%), and the risk of bleeding could be increased when both drugs are combined.[1] Although there is no clinical evidence of interaction between topical terbinafine and coumarins,[2] 2 cases with oral terbinafine and warfarin have been reported.[3,4] We present a case of a possible interaction between topical terbinafine and acenocoumarol.

Case Report. In August 2008, a 71-year-old white man presented with pain in his left calf, inflammation, petechiae, and bleeding lesions on his back and scalp. He had previously been diagnosed with chronic gastritis, arterial hypertension, dyslipidemia, and noninsulin-dependent diabetes mellitus and had been receiving acenocoumarol treatment for atrial fibrillation since 2004. He reported no significant changes in his diet or treatment (diltiazem 60 mg twice daily, lansoprazole 30 mg twice daily, atorvastatin 20 mg once daily, metformin 850 mg 3 times daily). Nine months before the symptoms appeared, he was diagnosed with seborrheic dermatitis on his head and back, for which he was treated with topical ciclopirox olamine 1.5% and mometasone furoate 0.1%, without improvement. In July 2008, the patient had begun treatment with topical terbinafine (1% Lamisil spray solution) once daily. Monthly international normalized ratio (INR) values with 13 mg of acenocoumarol per week as maintenance dose over the past year had been between 2.0 and 3.0 (target anticoagulation level). After 15 days of terbinafine treatment, he developed the symptoms previously described. At presentation, a blood sample via venipuncture was evaluated; his INR readings were greater than 8. Acenocoumarol and terbinafine were stopped and a single dose of phytonadione 10 mg was given. When the patient's INR went below the therapeutic range, subcutaneous bemiparin 5000 IU daily was initiated. After 6 days, acenocoumarol at a dose of 13 mg/week was restarted. After 1 week, INR readings were within the therapeutic range. Liver function tests were normal. After 12 months, INR monthly controls values were stable. The Horn Drug Interaction Probability Scale indicated a possible interaction between terbinafine and acenocoumarol.[5]

Discussion. In patients treated concurrently with oral terbinafine and warfarin, Warwick and Corrall[3] reported an increase in INR levels, while Gupta and Ross[4] reported a decrease. However, other authors have observed no interaction between these drugs.[6]

In our case, 2 mechanisms might explain this interaction. First, the drugs involved are extensively bound to plasma proteins. Introduction of topical terbinafine could have produced a displacement of acenocoumarol from plasma protein-binding sites. This may be clinically relevant in the elderly, in whom serum protein binding decreases. Visser et al.[6] have reported that men and older patients treated with antifungal agents and coumarins have a higher bleeding risk. Second, despite the fact that acenocoumarol is mainly metabolized by CYP2C9, other isozymes could also be involved.[6] It is possible that terbinafine, an inhibitor of CYP2D6, decreased the clearance of diltiazem, which is mebtabolized by CYP2D6.[6] Therefore, diltiazem, a potent inhibitor of CYP3A4, may have decreased the clearance of acenocoumarol (weakly mebtabolized by CYP3A4).[7] At the time of writing, this theory had not been confirmed.

In conclusion, it is not well known what percentage of topical terbinafine is absorbed nor the role of drugs, factors, or mechanisms involved in this interaction. Further research must address these questions. Therefore, acenocoumarol should be closely monitored while a patient is using terbinafine spray.

José Antonio Morales-Molina PhD
Clinical Pharmacist
Pharmacy Department
Empresa Pública Hospital de Poniente
Ctra. de Almerimar s/n
04700 El Ejido
Almería, Spain
fax 34 950 02 25 99
joseantonio.morales@ephpo.es

M Angustias Molina Arrebola PhD
Clinical Hematologist
Hematology Department
Empresa Pública Hospital de Poniente

Pedro Acosta Robles PharmD
Director Pharmacist
Pharmacy Department
Empresa Pública Hospital de Poniente

José Canto Mangana PharmD
PhD Candidate
Hospital Pharmacy Resident
Pharmacy Department
Empresa Pública Hospital de Poniente

Financial disclosure: None reported

Published Online, 20 Oct 2009, *theannals.com*
DOI 10.1345/aph.1M299

REFERENCES

1. DRUGDEX System. Terbinafine. Greenwood Village, CO: Thomson Micromedex Healthcare Series, expires 2009 December 31 (accessed 2009 Aug 18).
2. Gantmacher J, Mills-Bomford J, Williams T. Interaction between warfarin and oral terbinafine: manufacturer does not agree that interaction was with terbinafine (letter). BMJ 1998;317:205.
3. Warwick JA, Corrall RJ. Drugs points: serious interaction between warfarin and oral terbinafine (letter). BMJ 1998;316:440.
4. Gupta AK, Ross GS. Interaction between terbinafine and warfarin. Dermatology 1998;196:266-7. DOI 10.1159/000017890
5. Horn JR, Hansten PD, Chan L-N. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother 2007;41:674-80. Epub 27 Mar 2007. DOI 10.1345/aph.1H423
6. Visser LE, Penning-van Beest FJA, Harrie Kasbergen AA, et al. Overanticoagulation associated with combined use of antifungal agents and coumarin anticoagulants. Clin Pharmacol Ther 2002;71:496-502. DOI 10.1067/mcp.2002.124470

7. Sutton D, Butler AM, Nadin L, Murray M. Role of CYP3A4 in human hepatic diltiazem *N*-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. J Pharmacol Exp Ther 1997;282:294-300.

Evaluation of Pharmacist Use and Perception of Wikipedia as a Drug Information Resource

TO THE EDITOR: Approximately 80% of pharmacists use the Internet to obtain drug information.[1] Wikipedia, often found at the top of Internet search results, is a free-access, collaborative, online encyclopedia that can be edited by anyone.[2] Incidents of vandalism have occurred, since the site allows anyone to contribute. For example, an incident occurred in which a fake biography was created as a joke to implicate prominent writer and journalist John Seigenthaler for the assassination of John F Kennedy. It took about 4 months until the fake biography was detected and deleted by Wikipedia.[3] Although Wikipedia does have an internal quality review, the ability of internal editors to find and correct erroneous information may not be timely. As reported by Clauson et al.,[4] the information found on Wikipedia may not be complete and accurate, especially in regard to drug information. Published data regarding pharmacists' use of Wikipedia to obtain drug information is lacking. Therefore, the objective of this study was to measure pharmacists' use and perception of Wikipedia for obtaining drug information.

Seventy-eight state pharmacy associations in the US were contacted between February 2 and March 14, 2009, and requested to forward a link to an electronic questionnaire (Appendix I) to their pharmacist members. Forty-two percent (33/78) of the state pharmacy associations, representing 66% of states (33/50), participated. A total of 38,110 emails were sent, and 1067 questionnaires were completed, resulting in a 3% response rate. Eleven questionnaires were excluded because they were from students. Fifty-four percent (572/1056) of respondents were male, the mean age was 48 years (range 23–86 y), and mean time in practice was 23 years (0–65 y). Of the respondents, 52% had a bachelor's degree, 40% had a PharmD degree, and 9% had other degrees (eg, PhD, Master's). The majority of respondents did not have residency training (78%), with most practicing in either retail (40%) or hospital (37%) pharmacy settings.

Thirty-five percent (369/1056) of respondents reported use of Wikipedia. Of the 687 who did not report use of Wikipedia, 51% (351/687) indicated that they do not use Wikipedia because they have other resources available. Other reasons for not using Wikipedia included lack of trust (27%; 183/687) or lack of familiarity with the site (11%; 75/687). In regard to their perception of Wikipedia, 19% (69/369) of users reported that they trusted Wikipedia, 12% (43/369) indicated that they would recommend Wikipedia to other pharmacists, and 7% (25/369) would recommend Wikipedia to consumers/patients.

In terms of using Wikipedia specifically to obtain drug information, 28% (105/369) reported using it for this purpose, with the majority of these respondents reporting use of Wikipedia to identify medication indications. Of concern, only 28% (29/105) of the respondents who reported using Wikipedia to obtain drug information were familiar with who edits and manages the Web site. This study is limited by a low response rate and the fact that only pharmacists who were members of state pharmacy associations received the survey; also, not all areas of pharmacy practice were represented.

In conclusion, although the majority of respondents reported that they do not use Wikipedia as a drug information resource, only one third of pharmacists who reported use of Wikipedia for drug information were aware that anyone can edit the information. These results warrant an effort to educate pharmacists about the limitations and appropriate use of online resources for drug information.

Laurie Brokowski PharmD

At time of writing,
Drug Information Resident
School of Pharmacy and Pharmaceutical Sciences
Purdue University
West Lafayette, Indiana
now, Clinical Pharmacist
Veterans Affairs Northern Indiana Health Care System
Marion, Indiana 46953
fax 765/677-5158
laurie.brokowski@va.gov

Appendix I. Electronic Questionnaire

1.	Gender:	☐ M ☐ F	
2.	Age:		
3.	Highest degree:	☐ BS ☐ PharmD ☐ Other_____	
4.	Residency training:	☐ PGY1 ☐ PGY2 ☐ both ☐ none	
5.	Years in practice:		
6.	Practice setting:	☐ Retail ☐ Hospital ☐ Industry ☐ Academia ☐ Ambulatory ☐ Long term care ☐ Other:_____	
7.	Do you use Wikipedia?	☐ Yes ☐ No	
	a) If answer is "No": Why don't you use Wikipedia? *(end of Wikipedia questions)*	☐ Never heard of it ☐ I do not trust it	☐ I do not need to use it, because I have other resources available ☐ Other _____
	b) If answer is "Yes": What kind of drug information do you use from Wikipedia?: *(move to question 8)*	☐ Administration ☐ Contraindications ☐ Drug interactions ☐ Mechanism of action ☐ Other	☐ Adverse drug reactions ☐ Dosage ☐ Indications ☐ Pregnancy/Lactation ☐ I do not use Wikipedia for drug information
8.	Do you trust Wikipedia?	☐ Yes ☐ No ☐ Not Sure	
9.	Would you recommend the use of Wikipedia to other pharmacists?	☐ Yes ☐ No ☐ Not Sure	
10.	Would you recommend the use of Wikipedia to customers/patients?	☐ Yes ☐ No ☐ Not Sure	
11.	Do you know who edits and manages Wikipedia?	☐ Yes ☐ No ☐ Not Sure	

Amy Heck Sheehan PharmD
Associate Professor of Pharmacy Practice
School of Pharmacy and Pharmaceutical Sciences
Purdue University

Financial disclosure: None reported

Published Online, 20 Oct 2009, *theannals.com*
DOI 10.1345/aph.1M340

REFERENCES

1. Hailemskel B, White DP, Lakew DG, Thompson M, Wutoh AK. Internet as a drug information resource (abstract). ASHP Midyear Clinical meeting. 2001;36:p-404e.
2. Wikipedia. Wikipedia: about: the free encyclopedia. http://en.wikipedia.org/wiki/Wikipedia:About (accessed 2008 Dec 23).
3. Wikipedia. Wikipedia biography controversy. http://en.wikipedia.org/wiki/John_Seigenthaler_Sr._Wikipedia_biography_controversy (accessed 2009 Jun 11).
4. Clauson KA, Polen HH, Boulos MNK, Dzenowagis JH. Scope, completeness, and accuracy of drug information in Wikipedia. Ann Pharmacother 2008;42:1814-21. Epub 18 Nov 2008. DOI 10.1345/aph.1L474

Comment: Fatal Intracranial Bleed Potentially Due to a Warfarin and Influenza Vaccine Interaction

TO THE EDITOR: We read with great interest the case report by Carroll and Carroll[1] regarding a possible influenza vaccine–warfarin interaction. This report has the potential to influence influenza vaccine utilization for patients on warfarin. We address some issues that may have affected the patient's anticoagulation status that these authors did not fully address.

The patient was classified as "relatively stable" on warfarin. The American College of Chest Physicians (ACCP) recommends that stable international normalized ratios (INRs) be monitored every 4 weeks, with those not stable to be followed more frequently.[2] During the 6 months documented, this was not a stable record due to variable and multiple out-of-range INRs.

The patient's use of tobacco, alcohol, and over-the-counter products were ruled out as contributing factors. However, nutritional information was not provided regarding potentially interacting foods or beverages such as grapefruit, cranberries, or vitamin K–containing nutrients.[3]

This patient had low hemoglobin and hematocrit readings 1 year prior to the event, with a further decrease in both indices 1 month prior to his hemorrhage. Whether the decreases were due to progression of iron-deficiency anemia, anemia of the elderly, or to an underlying chronic bleed should be considered, especially in light of lower gastrointestinal bleeding documented 2 days prior to admission. A chronic gastrointestinal bleed seems possible, given the patient's history of gastroesophageal reflux disease, concomitant use of celecoxib, chronically low hemoglobin and hematocrit levels, and rectal bleeding prior to admission. Laboratory results indicated low serum protein and albumin by the time the INR was 15. These had been normal 1 month earlier; whether this signaled an undiagnosed illness is also unknown.

Carroll and Carroll[1] outlined previous reports of potential interactions between warfarin and influenza vaccination, but little critical evaluation was provided. Our brief review of these reports found no INR elevations as high as that observed in their case. Among the case reports cited by Carroll and Carroll, we found a consistent failure of the original reports to rule out confounding factors. In addition, a 2005 systematic review on warfarin interactions identified only 3 warfarin–influenza vaccine interaction studies that met their quality criteria: 2 reported no significant interaction, and 1 reported inhibition of warfarin effect but only in an elderly subgroup, based on post hoc analysis. The review specifically noted a need for analysis based on large administrative databases examining this and other possible drug interactions with warfarin.[4] The recent large database study listed by Carroll and Carroll (5167 subjects receiving warfarin and influenza and/or other vaccines),[5] as well as 2 other more recent cited reports with relatively rigorous study designs,[6,7] all reported no significant effect of influenza vaccine on INRs, nor were major bleeding episodes reported.

Past influenza vaccination in this patient was not associated with this reaction, giving negative answers on questions 5 and 6 of the Horn Drug Interaction Probability Scale (DIPS).[8] There are several other alternative contributing causes for this event, so question 7 of the DIPS is also negative. Without further screening to rule out these confounding factors, it seems premature to isolate influenza vaccination as the culprit. This report may influence influenza vaccination decisions for this high-risk population. It is important to rule out potential changes in the patient's nutritional status and a possible undiagnosed underlying concomitant illness as alternative contributing factors.

Alan WY Chock PharmD
Assistant Professor of Pharmacy Practice
School of Pharmacy and Health Professions
Creighton University
2500 California Plaza
Omaha, Nebraska 68178
fax 402/280-1268
chock@creighton.edu

Kathleen A Packard PharmD BCPS
Assistant Professor of Pharmacy Practice
School of Pharmacy and Health Professions
Creighton University

Linda K Ohri PharmD MPH
Associate Professor of Pharmacy Practice
School of Pharmacy and Health Professions
Creighton University

Financial disclosure: None reported

Published Online, 20 Oct 2009, *theannals.com*
DOI 10.1345/aph.1L413a

REFERENCES

1. Carroll DN, Carroll DG. Fatal intracranial bleed potentially due to a warfarin and influenza vaccine interaction. Ann Pharmacother 2009;43:754-60. Epub 31 Mar 2009. DOI 10.1345/aph.1L413
2. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2008;133:160-98.
3. Package insert. Coumadin (warfarin sodium). Princeton, NJ: Bristol-Myers Squibb, April 2006. www.accessdata.fda.gov/drugsatfda_docs/label/2006/009218s102lbl.pdf (accessed 2009 Jul 21).
4. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Int Med 2005;165:1095-106.
5. Jackson ML, Nelson JC, Chen RT, Davis RL, Jackson LA, for the Vaccine Safety Datalink investigators. Vaccines and changes in coagulation parameters in adults on chronic warfarin therapy: a cohort study. Pharmacoepidemiol Drug Saf 2007;16:790-6. DOI 10.1002/pds.1386
6. Lorio AM, Camilloni B, Basileo M, et al. Influenza vaccination in patients on long-term anticoagulant therapy. Vaccine 2006;24:6624-8.
7. MacCallum P, Madhani M, Mt-Isa S, Ashby D. Lack of effect of influenza immunisation on anticoagulant control in patients on long-term warfarin. Pharmacoepidemiol Drug Saf 2007;16:786-9. Epub 17 Nov 2006. DOI 10.1002/pds.1347
8. Horn JR, Hansten PD, Chan L-N. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother 2007;41:674-80. Epub 27 Mar 2007. DOI 10.1345/aph.1H423

AUTHORS' REPLY: We appreciate the interest and comments provided by Chock et al. regarding our article. They have raised several questions that necessitate a response.

We agree that this case report has the potential to influence use of influenza vaccination for patients on warfarin. However, we never advocated that patients taking warfarin not be vaccinated with the influenza vaccine. We did advocate that healthcare providers implement more frequent INR evaluations in the 4–6 weeks following influenza vaccination, given the serious outcome we observed in our patient and the current literature available on this subject. We believe that this is a prudent and realistic practice to incorporate in patients taking warfarin who are immunized with inactivated influenza vaccine.

They commented on our classification of the patient's INR as "relatively stable." We agree, the patient should have been monitored every 4 weeks per the recommendations by the ACCP. However, the patient failed to return for routine INR monitoring on that schedule. We still believe that the INR was relatively stable in regard to fluctuations above and below the targeted INR of 2–3, with the highest value of 4.7 and the lowest value of 1.4 in the 6 months prior to the event. Our patient was slightly below the average (in days) reported in community practice (56.7%) and clinical trials (66.4%).[1]

Chock et al. also commented that the nutritional information was never provided for foods and beverages that could be contributing factors for this patient's significantly elevated INR. The patient's wife denied other significant changes that might have impacted the INR at the time of the event, and these included dietary changes (both for foods and beverages). It was not possible to elucidate any more specific information.

Chock et al. commented on the potential impact of chronic anemia and gastrointestinal bleed in our patient. We have found no evidence that links these conditions to a sudden, drastic increase in a patient's INR. The focus here is not on whether the patient had anemia, but rather on the timing between administration of an influenza vaccine and extreme INR elevation.

There was also concern mentioned by Chock et al. regarding the low serum protein and albumin levels at the time of presentation. They believe that these could be related to an undiagnosed illness. While that is a possibility, we believe that the lower protein and albumin levels were more likely related to the hemorrhaging and acute physiological stress the patient was experiencing at the time of presentation to the emergency department.[2,3] Considering the grave condition of the patient, other underlying illnesses were not evaluated at the time of presentation.

Chock et al. questioned our degree of critical evaluation of the literature related to warfarin and inactivated influenza vaccine. We believe that our critical evaluation was sufficient and this was affirmed through *The Annals'* peer review process. Due to this being a case report, an extensive evaluation in print was beyond the scope of the article. However, we did discuss the more clinically relevant studies and included Table 1 as a complete overview of the available literature.

We agree with Chock et al. that there are no reports in the literature of INR elevations as high as in this case. There are inherent limitations to the current literature as discussed in our original case report (small sample sizes, variations in annual inactivated influenza vaccine formulations). However, we do not think that these nullify this case report and its findings.

Finally, they questioned our DIPS score for this case report. In regard to their comment regarding our observation that the previous year's influenza vaccination did not result in a similar reaction (significantly elevated INR), one possible explanation is that, if there was an elevation in the INR and the patient was without symptoms, it could have gone undetected since his INR was not assessed until 7 weeks after vaccination the previous year. Reports have been conflicting, but both significant decreases and increases have been observed most frequently in the 2 weeks after vaccination.[4,5] In addition, a few authors have suggested that the interaction between warfarin and inactivated influenza vaccination may be impacted by variations in the vaccine preparation/formulation each year.[4,6] Our patient would have had 2 different inactivated influenza preparations from the year prior to the event when he was vaccinated to the year of the event when he was vaccinated.

Chock et al. also believe that there were other potential contributing causes that should be reflected in adjusting the DIPS score. We ruled out as many "other contributing factors" as possible in this patient, as discussed previously. Based on the factors mentioned above, we believe that our original DIPS score was accurate for this patient.

Again, we are not advocating that patients who are receiving warfarin should avoid the inactivated influenza vaccine. However, it does appear prudent to monitor INR values more regularly during the 4–6 weeks following vaccination.

Dana G Carroll PharmD BCPS

Clinical Associate Professor
Harrison School of Pharmacy
CCHS University Medical Center
PO Box 870374
Tuscaloosa, Alabama 35847
fax 205/348-2889
dgc0001@auburn.edu

Doug N Carroll PharmD BCPS

Clinical Associate Professor
Harrison School of Pharmacy

Financial disclosure: None reported

Published Online, 20 Oct 2009, *theannals.com*
DOI 10.1345/aph.1L413b

REFERENCES

1. Van Walraven C, Jennings A, Oake N. Effect of study setting on anticoagulation control: a systematic review and meta-regression. Chest 2006; 129:1155-66. DOI 10.1378/chest.129.5.1155
2. Blood studies. In: Pagana KD, Pagana TJ, eds. Mosby's manual of diagnostic and laboratory tests. 3rd ed. St. Louis, MO: Mosby Elsevier, 2006: 434-40.
3. Warner EA, Herold AH. Interpreting laboratory tests. In: Rakel RE, eds. Rakel: textbook of family medicine. 7th ed. Philadelphia, PA: Saunders Elsevier, 2007:1. www.mdconsult.com/das/book (accessed 2009 Aug 11).
4. Bussey HI, Saklad JJ. Effect of influenza vaccine on chronic warfarin therapy. Drug Intell Clin Pharm 1988;22:198-201.
5. Paliani U, Filippucci E, Gresele P. Significant potentiation of anticoagulation by flu-vaccine during the season of 2001–2002. Haematologica 2003;88:599-600.
6. Weibert RT, Lorentz SM, Norcross WA, Klauber MR, Jagger PI. Effect of influenza vaccine on patients receiving long-term warfarin therapy. Clin Pharm 1986;5:499-503.

Comment: Evaluation of the Modified Diet in Renal Disease Equation for Calculation of Carboplatin Dose

TO THE EDITOR: Shord et al.[1] reported similar frequencies of thrombocytopenia, neutropenia, and the need for dosage modifications in their comparison of carboplatin doses based on traditional serum creatinine (SCr)–based equations (ie, Cockcroft-Gault, Jelliffe) versus the Modification of Diet in Renal Disease (MDRD) equation. However, they concluded that the estimated glomerular filtration rate (GFR) and the MDRD equation should not be used to estimate carboplatin doses until more data are available.

We previously found that carboplatin dosing based on the MDRD equation was associated with precision better than and bias similar to that of the Cockcroft-Gault equation, compared with measured GFR.[2] More recent studies also support these findings. Poole et al.[3] reported no significant deviation from "true" carboplatin dose (based on measured GFR) in similar proportions of patients between the MDRD (58%) and the Cockcroft-Gault equations (63%). Two other studies also reported

good correlation in carboplatin dose between the 2 equations (correlation coefficient of 0.73 and 0.88).[4,5]

The MDRD equation allows for the automatic reporting of estimated GFR as part of renal biochemistry. This may reduce potential calculation errors. Shord et al. showed that any discordance between the 2 equations is unlikely to be clinically significant for the patient with average body size (body surface area ~1.8 m^2) and renal function (SCr ~1.0 mg/dL). Therefore, it seems reasonable to use either equation to guide carboplatin dosing if measured GFR is not available, provided that the same estimation method is used during a particular course of treatment. A similar recommendation has been made by the British National Formulary, as well as by expert consensus in Australia and New Zealand.[6]

Mário L de Lemos PharmD MSc (Oncol)
Provincial Drug Information Coordinator
Pharmacy Department
British Columbia Cancer Agency
600-750 West Broadway
Vancouver, British Columbia, Canada
fax 604/708-2024
mdelemos@bccancer.bc.ca

Linda Hamata BSc(Pharm)
Staff Pharmacist
Pharmacy Department
British Columbia Cancer Agency

James Conklin BSc(Pharm) ACPR
Staff Pharmacist
Pharmacy Department
British Columbia Cancer Agency

Financial disclosure: None reported

Published Online, 20 Oct 2009, *theannals.com*
DOI 10.1345/aph.1L446a

REFERENCES

1. Shord SS, Bressler LR, Radhakrishnan L, Chen N, Villano JL. Evaluation of the Modified Diet in Renal Disease equation for calculation of carboplatin dose. Ann Pharmacother 2009;43:235-41. Epub 3 Feb 2009. DOI 10.1345/aph.1L446
2. de Lemos ML, Hsieh T, Hamata L, et al. Evaluation of predictive formulae for glomerular filtration rate for carboplatin dosing in gynecological malignancies. Gynecol Oncol 2006;103:1063-9. DOI 10.1016/j.ygyno.2006.06.024
3. Poole SG, Dooley MJ, Rischin D. Calculating carboplatin doses using the 4-variable Modification of Diet in Renal Disease (4-v MDRD) estimate of glomerular filtration rate (GFR) in the Calvert formula (abstract 2521). 2007 ASCO Annual Meeting Proceedings. J Clin Oncol 2007;25 (Jun 20 suppl):2521.
4. Cooper AV, Roques TW. Can MDRD (Modification of Diet in Renal Disease) be used to estimate GFR in patients receiving carboplatin (abstract)? Clin Oncol (R Coll Radiol) 2007;19(3):S27. DOI 10.1016/j.clon.2007.01.349
5. Barry A, O'Cearbhaill R, Griffin D, Donnellan P, Keane M, Grimes H. Evaluation of carboplatin dosage based on 4-variable modification of diet in renal disease equation. Ir J Med Sci 2009;178:301-7. Epub 11 Nov 2008. DOI 10.1007/s11845-008-0250-z
6. Jones GR, Mathew T, Johnson D, Peake M. Implementation of the routine reporting of eGFR in Australia and New Zealand. Scand J Clin Lab Invest Suppl 2008;241:23-9. DOI 10.1080/00365510802144953

AUTHORS' REPLY: de Lemos et al. correctly stated that our results demonstrated a similar frequency of thrombocytopenia, neutropenia, and need for dose modifications when using traditional SCr-based equations versus the MDRD equation. As noted in our discussion, at least 2 other studies attempted to define a clinically relevant difference but did not define the clinical consequence of using different estimates of GFR in the calculation of carboplatin renal clearance and dose.[1,2] Our study emphasized clinical outcomes (ie, toxicity) rather than precision or correlation between different equations and actual GFR. Based on the published literature and our results, we concluded that further investigation is warranted before the MDRD equation is routinely incorporated into clinical practice. Our reservations stem from the fact that area under the curve achieved using the various estimates of GFR, including the MDRD equation, has not been examined prospectively. In addition, the MDRD equation was developed for patients with chronic kidney disease. It is apparent that traditional SCr-based estimates frequently underestimate GFR, potentially leading to underdosing, and likely stray from the intended dose based on the Calvert formula. Our study demonstrates that the clinical consequences (as defined in our study) are similar when using the various equations. Thus, we believe that additional investigation is warranted and that clinical practice need not be changed until research demonstrates that the MDRD equation permits the calculation of a carboplatin dose that results in the intended exposure and improves the clinical outcomes of patients treated with this cytotoxic drug.

Stacy S Shord PharmD BCOP
at time of writing,
Assistant Professor
College of Pharmacy (M/C 886)
University of Illinois at Chicago
now, Reviewer
US Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology
Division of Clnical Pharmacology 5
Silver Spring, Maryland
fax 301/796-9736
stacy.shord@fda.hhs.gov

Linda R Bressler PharmD BCOP
Clinical Associate Professor
College of Pharmacy
University of Illinois at Chicago

J Lee Villano MD PhD
Assistant Professor
College of Medicine
University of Illinois at Chicago

Financial disclosure: None reported

Published Online, 20 Oct 2009, *theannals.com*
DOI 10.1345/aph.1L446b

The opinions and information in this letter are those of the authors and do not represent the views and/or policies of the US Food and Drug Administration.

REFERENCES

1. de Lemos ML, Hsieh T, Hamata L, et al. Evaluation of predictive formulae for glomerular filtration rate for carboplatin dosing in gynecological malignancies. Gynecol Oncol 2006;103:1063-9. DOI 10.1016/j.ygyno.2006.06.024
2. Poole SG, Dooley MJ, Rischin D. Calculating carboplatin doses using the 4-variable Modification of Diet in Renal Disease (4-v MDRD) estimate of glomerular filtration rate (GFR) in the Calvert formula (abstract 2521). 2007 ASCO Annual Meeting Proceedings. J Clin Oncol 2007;25 (Jun 20 suppl):2521.