Q & A Column , 1/14

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How to calculate the correction factor for blood drawn in an ACD tube

Malaria thick and thin smear for travel visa purposes

Coenzyme Q10 and warfarin/INR interference

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Q. I read a question and answer in the April 2001 CAP TODAY about platelet clumping on EDTA and whether vortexing is an acceptable procedure. A common solution suggested was to redraw the specimen into sodium citrate or acid citrate dextrose (ACD). How do you calculate the correction factor for blood drawn in an ACD tube? Our lab has an old procedure for ACD correction, and it is to divide the RBC of the EDTA tube by the RBC count of the ACD tube. I don't have any reference for this and would appreciate information.

A. The 2001 Q&A by Steven Kroft, MD, discusses approaches for obtaining an accurate platelet count, including vortexing and alternative anticoagulants (sodium citrate, ACD), when platelet aggregates/agglutinates are present in the EDTA anticoagulated specimen. These platelet clumps can result in "pseudothrombocytopenia" if this artificially low platelet count is erroneously reported by the laboratory. As Dr. Kroft mentioned, if vortexing does not adequately normalize the platelet count, an alternative anticoagulant can be used since many of these patients have EDTA-dependent antibodies that result in platelet clumping. The most commonly used alternative anticoagulant for this purpose is sodium citrate. In comparison to an EDTA sample, it is well known that sodium citrate results in 10 percent dilution of the blood sample due to the volume of the liquid anticoagulant. As such, platelet counts will be 10 percent lower in sodium citrate, and thus a conversion factor of 1.1 is used to calculate a platelet count from sodium citrate.

A conversion factor for ACD tubes is not as well established, perhaps due to differences among ACD tubes of various sizes or from different manufacturers, or both. In any case, a similar calculation reflecting the difference in sample dilution when compared to EDTA is the appropriate method to accurately correct the platelet count in ACD. RBC count is one parameter that can be used for this purpose, since the ratio of RBC in EDTA to RBC in ACD should reflect any dilutional difference between

the anticoagulants. This ratio can then be multiplied by the ACD platelet count according to the following formula to obtain the ACD corrected platelet count:

1. Lippi G, Plebani M. EDTA-dependent pseudothrombocytopenia: further insights and recommendations for prevention of a clinically threatening artifact. *Clin Chem Lab Med.* 2012;50(8):1281–1285.
2. Lombarts AJ, de Kieviet W. Recognition and prevention of pseudothrombocytopenia and concomitant pseudoleukocytosis. *Am J Clin Pathol.* 1988;89:634–639.
3. Onder O, Weinstein A, Hoyer LW. Pseudothrombocytopenia caused by platelet agglutinins that are reactive in blood anticoagulated with chelating agents. *Blood.* 1980;56:177–182.
4. Payne BA, Pierre RV. Pseudothrombocytopenia: a laboratory artifact with potentially serious consequences. *Mayo Clin Proc.* 1984;59:123–125.
5. Shreiner DP, Bell WR. Pseudothrombocytopenia: manifestation of a new type of platelet agglutinin. *Blood.* 1973;42: 541–549.

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Q. Our laboratory recently received an order for malaria thick + thin smear for an asymptomatic patient for the purpose of travel visas. The patient's travel history is not readily available to the lab, and it appears some countries do require a "malaria test" before issuing visas to visitors. I have concerns about the value of a thick/thin smear in this clinical setting. Would other laboratory screening methods be more appropriate in asymptomatic, likely low-risk patients?

A. We agree with your assessment that testing for malaria in an asymptomatic individual, especially without a relevant travel history, has questionable benefit. However, if it is required for visa purposes, then we would recommend performing either a traditional thick film or a malaria PCR assay. In general, malaria PCR has greater sensitivity than conventional blood film morphology and therefore would have the highest likelihood of detecting very low levels of parasitemia, although its availability is limited to reference labs and the Centers for Disease Control and Prevention. You may wish to check the requirements of the specific country that is requiring this testing to ensure that it does not have a preferred test. Thick and thin blood films are probably acceptable in most if not all cases.

Sensitivity of thick blood film for malaria detection

1. Ross R. Ross: An improved method for the microscopical diagnosis of intermittent fever. *Lancet.* 1903;161:86.
2. Warhurst DC, Williams JE. ACP Broadsheet no 148. July 1996. Laboratory diagnosis of malaria. *J Clin Pathol.* 1996; 49(7):533–538.
3. Ochola LB, Vounatsou P, Smith T, Mabaso ML, Newton CR. The reliability of diagnostic techniques in the diagnosis and management of malaria in the absence of a gold standard. *Lancet Infect Dis.* 2006; 6(9):582–588.

Sensitivity of malaria PCR versus blood films

1. Perandin F, Manca N, Calderaro A, et al. Development of a real-time PCR assay for detection of Plasmodium falciparum, Plasmodium vivax, and Plasmodium ovale for routine clinical diagnosis. *J Clin Microbiol.* 2004;42(3):1214–1219.
2. Singh B, Bobogare A, Cox-Singh J, et al. A genus- and species-specific nested polymerase chain reaction malaria detection assay for epidemiologic studies. *Am J Trop Med Hyg.* 1999;60(4):687–692.
3. Cnops L, Jacobs J, Van Esbroeck M. Validation of a four-primer real-time PCR as a diagnostic tool for single and mixed Plasmodium infections. *Clin Microbiol Infect.* 2011;17(7):1101–1107.

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Q. Patients who take statins may deplete their levels of CoQ10 (Coenzyme Q10), and therefore many of these patients are now taking CoQ10 supplements. Can CoQ10 supplements affect the level of Coumadin (that is, the INR)?

A. Statins, commonly used to treat hypercholesterolemia, can cause myalgia. There have been suggestions that statins cause muscle injury by lowering levels of Coenzyme Q10, which has a key role in mitochondrial respiration. The literature is sparse and the results are mixed regarding the ability of CoQ10 administration to reduce muscle symptoms. Nevertheless, patients may choose to take CoQ10 as a dietary supplement in an attempt to reduce myalgia caused by statins. Supplementation of CoQ10 has also been studied in heart failure and numerous other health conditions, but, again, a clear role for replacement has not been defined.

The interaction of warfarin with food, drugs, and some herbal products has been well recognized. In a systematic overview of publications related to warfarin interactions with drug, food, and supplements,1 there were 92 substances with a probable or highly probable level of evidence supporting the potentiation or inhibition of warfarin. However, few studies have focused on CoQ10 and warfarin interactions/INR interference. In an animal study, Zhou, et al.,2 suggested that the accelerated metabolism of warfarin enantiomers (S and R forms) with concurrent CoQ10 treatment accounts for the reduced anticoagulant effect of warfarin in rats. The authors speculated that a moderate increase in the total clearance of warfarin enantiomers could occur with coadministration of CoQ10 in humans.

There are a few case reports of decreased INR after CoQ10 ingestion in humans.3 However, there is only one well-designed randomized, double-blind study in the literature evaluating CoQ10 and warfarin.4 A small group of patients on stable warfarin treatment for different indications participated in this crossover study. Subjects took CoQ10 (100 mg/day)/warfarin for four weeks, Ginkgo biloba/warfarin for four weeks, and placebo/warfarin for four weeks. There was no significant difference in INR for each combination. The authors concluded there was no

significant interference during the coadministration of warfarin and CoQ10 but remained cautious, recommending close monitoring of the INR in these patients.

In summary, the best available evidence suggests that CoQ10 does not affect INR in humans, but the results of this single randomized, double-blind study have not been confirmed in additional well-designed studies. Additionally, the dose and potency of CoQ10 supplements have not clearly been established, so it seems reasonable to closely monitor patients taking warfarin and CoQ10.

1. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med.* 2005;165(10):1095–1106.
2. Zhou Q, Zhou S, Chan E. Effect of coenzyme Q10 on warfarin hydroxylation in rat and human liver microsomes. *Curr Drug Metab.* 2005;6(2):67–81.
3. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet.* 1994;344(8933):1372–1373.
4. Engelsen J, Nielsen JD, Winther K. Effect of coenzyme Q10 and Ginkgo biloba on warfarin dosage in stable, long-term warfarin treated outpatients. A randomised, double blind, placebo crossover trial. *Thromb Haemost.* 2002;87(6):1075–1076.

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