

Warfarin use and dose adjustment in a patient with mitral valve replacement

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Abstract: Warfarin is an anticoagulant suppressing the synthesis of the specific vitamin K-dependent coagulation factors II, VII, IX and X as well as two vitamin K-dependent plasma proteins C and S. Warfarin therapy may bring about severe consequences including warfarin embryopathy associated with maternal warfarin ingestion, warfarin resistance, excessive anticoagulation and warfarin reversal. A 51-year-old female patient experienced warfarin resistance as well as subsequent excessive coagulation and warfarin reversal. With regulation of warfarin dosage and close monitoring of the international normalized ratio, she eventually obtained a proper target international normalized ratio with stable warfarin dose. The patient was more likely to have an acquired warfarin resistance. To regulate dietary habit might be a good solution for the resistance to this drug. In addition, individualized regimen for warfarin use should be established based on the conditions of individual patient including patient's age, gender, body surface area, dietary habit and target international normalized ratio, *etc.*

Keywords: international normalized ratio; warfarin; vitamin K.

INTRODUCTION

Warfarin is an anticoagulant suppressing the synthesis of the specific vitamin K-dependent coagulation factors II, VII, IX and X as well as two vitamin K-dependent plasma proteins C and S by interfering the vitamin K metabolism mediated γ -carboxylation process (Osinbowale *et al.*, 2009). Warfarin shows different pharmaceutical properties between the two enantiomers, R- and S-warfarin. R-warfarin is metabolized by several cytochrome P450 (CYP) isoforms including 1A2 and 3A4 and by nonspecific NADPH-dependent carbonyl reductases; whereas S-warfarin is metabolized by alternative isoforms such as CYP2C9. Therefore, the efficacy of warfarin is prevailed by S-warfarin metabolism as S-warfarin shows more intense drug effect than R-warfarin (Kaminsky and Zhang, 1997).

Without proper monitoring, warfarin coagulation may cause severe problems in several occasions (Banerjee *et al.*, 2012), which include warfarin embryopathy associated with maternal warfarin ingestion (Hou, 2004), warfarin resistance (Sinxadi and Blockman 2008; Osinbowale *et al.*, 2009), excessive anticoagulation (Banerjee *et al.* 2012) and warfarin reversal (Hanley, 2004). Besides, warfarin failure, a new thrombotic event or life-threatening bleeding despite a target prothrombin time (PT) and international normalized ratio (INR) (Osinbowale *et al.*, 2009), was once described but lack of further clarifications. Warfarin resistance is a phenomenon when the patients poorly respond to a cumulative dose of warfarin over time for a target INR (Qureshi *et al.*, 1981).

CLINICAL OBSERVATION

A 51-year-old female patient was referred to this hospital due to exertional chest distress and shortness of breath for 1 month. Her vital signs were normal, but a loud systolic murmur over the apex was audible. Transthoracic echocardiography revealed prolapse of the posterior leaflet of the mitral valve due to rupture of a major chorda tendinea. She underwent mitral valve replacement with a 25-mm St. Jude Medical prosthesis. She was uneventful postoperatively, but she did not respond to increasing warfarin dosages in terms of INR in the first postoperative week. Additional coagulants were therefore added. Aspirin 200 mg and clopidogrel 25 mg was supplemented to warfarin on PODs 8 and 9, respectively, but revealed no effect on promoting INR. Hence, low molecular weight heparin (LMWH) 4000 units subcutaneous injection twice daily, was prescribed since POD 10. INR began to show a slight increase on POD 15 and LMWH was stopped since POD 16. The maximal warfarin dose was 12.5 mg/day and 71.25 mg/week between PODs 11 and 17. However, excessive coagulation occurred on POD 18, for which warfarin was withheld for one day along with 10 mg of intravenous vitamin K₁. Her INR dropped to baseline and increased anticoagulant intensity was applied to her (Fig. 1). Without any signs of hemorrhage or embolic events, she was discharged with close INR surveillance and subsequent warfarin use in outpatient clinic. She eventually obtained a target INR with a daily warfarin dose of 3.75 mg. Meanwhile, the patient was advised to avoid vitamin K₁-rich dietary and products. She was doing well since then and was still on close follow-up.

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DISCUSSION

Pregnant patients are at an increased risk of thromboembolic events because they are physiologically hypercoagulable with increased coagulation factors, fibrinogen and platelet aggregation (Vitale *et al.*, 1999). Teratogenicity of warfarin has been well documented, especially with its use during 6-12 weeks of pregnancy. The incidence of teratogenicity varies from 5% to 15%. Maternal warfarin ingestion may cause fetal warfarin syndrome (warfarin embryopathy), most often present with hypoplastic nasal bone, dysplasia epiphysealis punctata, cacomelia and life-threatening respiratory distress syndrome (Hou, 2004). Abnormal developments of fetus due to maternal warfarin therapy also include renal agenesis or nonfunctioning kidneys, epiphosis, psychogenic seizures and Dandy-Walker malformation (Hall *et al.*, 1980; Hall, 1989). Spontaneous abortions or stillbirths may occur in approximately 16% and physical deformity in babies at birth may present in 15% (Abadi *et al.*, 2002). Therefore, hypodermic heparin should be administered as a substitute of oral warfarin when the woman with a mechanical heart valve prosthesis is pregnant. The timing of heparin treatment instead of warfarin is suggested the first trimester and the last 3 gestation-week of pregnancy, while warfarin use, in 13-37th gestation week (Lee *et al.*, 1986).

There have been several inhomogeneous definitions of warfarin resistance in the literature, a prolonged warfarin requirement of (1) >20 mg/day (Harrington *et al.*, 2008), (2) >105 mg/week or >15 mg/day (Osinbowale *et al.*, 2009), (3) >70 mg/week (Sinxadi and Blockman 2008), (4) ≥ 9 mg/day (Routledge *et al.*, 1998), (5) >9 mg/day (Parvizi *et al.*, 2011) and (6) patients poorly respond to a cumulative dose of oral warfarin (no substantial dose for warfarin requirement), for an adequate INR elevation to achieve therapeutic anticoagulation or failure to achieve therapeutic anticoagulation with this dose (Sharma *et al.*, 2007). Warfarin requirements vary markedly from one patient to another with 95% at 1-9 mg/day (Parvizi *et al.*, 2011). Although warfarin requirement ≥ 9 mg/day was taken as a diagnostic criterion of warfarin resistance (Parvizi *et al.*, 2011), a dose of 10 mg/day was considered as an adequate dose for most patients especially for individuals whose diets are high in vitamin K₁ (Jensen, 2008).

Warfarin resistance can be classified as acquired (patient's improper medication compliance, growing vitamin K₁ consumption, impaired warfarin absorption, enhanced clearance and drug/diet/herb interactions) and hereditary (Qureshi *et al.*, 1981). Hereditary resistance is rare and the genetic mechanisms are not well understood. It has been postulated that hereditary resistance might result from genetic factors by quick consumption (pharmacokinetic resistance), or inactivation

(pharmacodynamic resistance). CYP2C9 and VKORC1 gene polymorphisms, responsible for at least partly pharmacodynamics mechanism of warfarin resistance (Schwarz *et al.*, 2008), and heterozygous mutation or wild type T1173T genotype carriers other than the homozygous (D'Andrea *et al.*, 2005) have shown hypersensitivities to warfarin. Missense mutations of Val29Leu, Ala41Ser, Arg58Gly, Val66Met, Leu128Arg, Val145Ala and Asp36Tyr are also involved in hereditary warfarin resistance (Sinxadi *et al.*, 2008).

In the Western countries, a target INR of 2.0-3.0 was recommended for most indications including prosthetic mitral valve replacement (Banerjee *et al.*, 2012). In the past, more intense anticoagulation intensity with a prothrombin ratio of 1.5-2.0 and an INR of 2.0-3.0 was undertaken in our country that has caused high rates of embolic events and mortality in heart valve replacement patients. Since the mid of 1990's, a domestic consensus has proposed on a decreased anticoagulation intensity to an INR of 1.4-2.5, which has brought about significantly decreased hemorrhagic and mortality rates (Anonymous, 2010). Clinical observations by Song *et al.* (2007) revealed an optimal therapeutic target INR of 1.60-2.50 (prothrombin time 16-22s) in Chinese patients with a prosthetic heart valve, much lower than that of the patients in the Western countries. They also noted that INR varied with sex and dose of requirement, and INR was significantly elevated in September in most of the patients than in other months of the year.

A prospective study on warfarin disclosed no significant difference in patient's age, gender, or body weight between patient groups with different warfarin therapeutic doses. However, excessive anticoagulation (INR >3.0) may develop more commonly in patients with lower than those with higher therapeutic dosages (Wei, 2010). An observational study has investigated that cytochrome P450 2C9 (CYP2C9) allelic variant, the homozygous CYP2C9*3/CYP2C9*3 genotype, may also link to hyper-responsiveness to small doses of oral anticoagulants (warfarin or acenocoumarol) and a higher bleeding rate (Verstuyft *et al.*, 2003). Excessive anticoagulation can incur hemorrhage in any location of the body, but the most severe type would be intracerebral hemorrhage. There was a close dependency between INR and hemorrhage risks. The risk of hemorrhages would increase significantly when INR >4 and the risk went up sharply when INR >5 (Banerjee *et al.*, 2012). With an INR of 1.2-2.0 or 2.1-3.0, hematoma volumes did not differ; whereas patients with an INR of >3.0 showed a larger hematoma size. In addition, relations were found between larger hematoma size and intracerebral hemorrhagic site (either lobar or deep cerebral hemorrhages) and shorter time lapses between stroke onset and acquisition of brain computed tomographic scan (Flaherty *et al.*, 2008; Kim *et al.*, 2008).

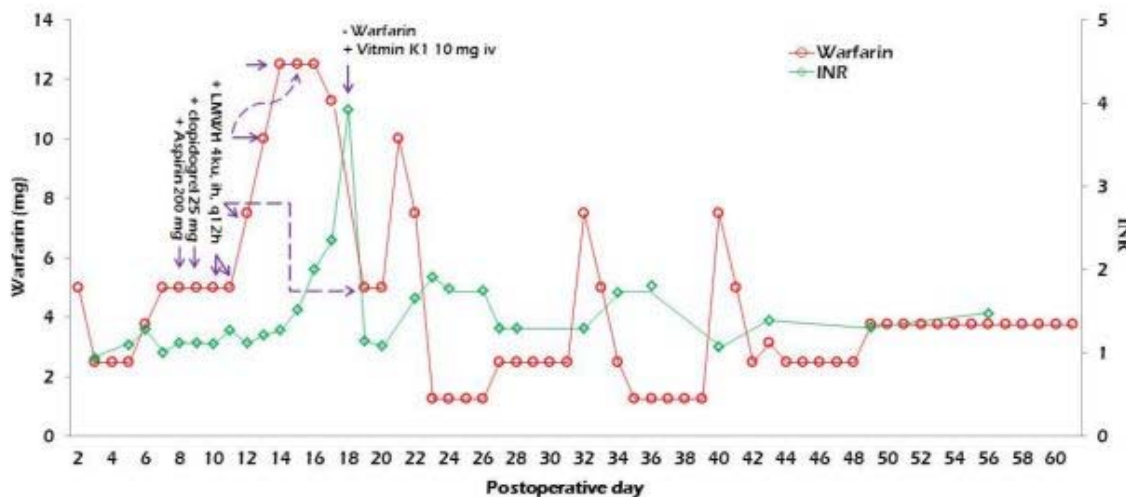


Fig. 1: A 2-month monitoring of international normalized ratio. *ih*: subcutaneous injection; *iv*: intravenous injection; INR: international normalized ratio; LMWH: low molecular weight heparin; q12h: every 12 hours.

Warfarin reversal can be undertaken in four ways: to withhold warfarin (ultraslow), to take oral vitamin K₁ (slow), to inject vitamin K₁ (prompt) and to infuse fresh frozen plasma (fast) or prothrombin complex concentrate (rapid) (Hanley, 2004). In patients with a mechanical heart valve, coagulant withhold could last for 1-2 weeks (Phan *et al.*, 2000), 4-6 weeks (Crawley *et al.*, 2000), or substitute therapy by intravenous unfractionated heparin (UFH) or subcutaneous LMWH (Butler and Tait, 1998; Leker and Abramsky, 1998). In patients with intracranial hemorrhage, warfarin withhold for 1-2 weeks might be enough for preventing intracranial hemorrhage expansion and timely interventional therapies (Wijdicks *et al.*, 1998).

Half of the patients had inadequate anticoagulation despite intensive INR monitoring. This is because platelet aggregation may occur and adhere on damaged perivalvular tissues as soon as cardiopulmonary bypass terminates. The prosthetic surface and blood stasis of the patients may activate the coagulation factors and enhance the thrombogenicity (Ambrosetti *et al.*, 2009).

A cumulative warfarin dosage towards 20 mg/day without INR elevation should raise suspicion about high vitamin K₁ intake (Goz *et al.*, 2006). A dietary vitamin K intake of 65-80 µg/day is an acceptable recommendation for the patients with warfarin use (Booth and Centurelli, 1999). Green leaf vegetable (Sharma *et al.*, 2007) and soya-bean, grape-kernel and olive oils contain abundant amount of vitamin K₁ (Bolton-Smith *et al.*, 2000), 150-300 g/100 g in soya-bean oil in comparison to 6-12 g/100 g in safflower oil (Bolton-Smith *et al.*, 2000). Herbal products, diet pills, nutritional supplements and antibiotics (including antituberculosis drugs) (Ambrosetti *et al.*, 2009) have potential warfarin interactions. Nevertheless, the dose-response relations of vitamin K with regard to warfarin therapy remain to be elaborated.

Increased resistance to warfarin as evidenced in rats has stepped up the pace of advent and application of the longer-acting and more potent superwarfarins, *i.e.*, the derivatives of 4-hydroxycoumarin (Hadler and Shadbolt, 1975). In humans, the half-life of warfarin varies between 17 and 37 hours (Bachmann and Sullivan, 1983). However, switch to alternative anticoagulants seems to be impossible in our country. There is no other reagent type of warfarin (warfarin injection) or other substitutes of oral anticoagulants (acenocoumarol) available. Acenocoumarol has been out of stock stealthily, we do not know, from which time. Therefore, the management of a warfarin resistance is very challenging for the physicians who were frustrated by short of drugs, and for the patients who are at an even higher risk of thromboembolic and (or) hemorrhagic event than before.

When encountering an abnormal INR during warfarin therapy, it has to bear in mind of miss or extra dosage, dietary change, undisclosed drug use and alcohol use. Lab error is of course another reason. With larger permitted INR range, supplemented use of alternative anticoagulants (aspirin, clopidogrel, UFH, or LWMH) to warfarin in order to maintain an adequate INR should be a prerequisite of warfarin resistance. Moreover, the duration of increased warfarin use in relation to has not been discussed previously. From the viewpoint of the present study, the duration of might be at least 5 days (3.3 times of half-life time of warfarin) of increased warfarin ≥9 mg/day. The present patient experienced warfarin resistance, excessive coagulation and warfarin reversal.

CONCLUSIONS

The patient was more likely to have an acquired warfarin resistance. To regulate dietary habit might be a good

solution for warfarin resistance in some occasions. In addition, individualized regimen for warfarin use should be established based on each patient's condition including patient's age, gender, body surface area, dietary habit and target INR intensity, etc.

REFERENCES

- Abadi S, Einarson A and Koren G (2002). Use of warfarin during pregnancy. <http://www2.cfpc.ca/cfp/2002/Apr/vol48-apr-clinical-1.asp>.
- Ambrosetti M, Ageno W, Calori A, Ferrarese S, Barosi A, Marchetti P, Salvato L and Sala A (2009). Fluctuations in warfarin dose response after heart valve surgery: Implications for cardiac rehabilitation. *Monaldi Arch. Chest Dis.*, **72**: 29-32.
- Anonymous (2010). Chinese low intensity anticoagulant therapy after heart valve replacement multi-center clinical study. *Chin J Clin Thorac Cardiovasc Surg.*, **17**: I0001-I0002.
- Bachmann KA and Sullivan TJ (1983). Dispositional and pharmacodynamic characteristics of brodifacoum in warfarin-sensitive rats. *Pharmacology*, **27**: 281-288.
- Banerjee SK, Saha K and Maitra S (2012). Warfarin toxicity management. http://apiindia.org/pdf/medicine_update_2012/hematology_and_oncology_06.pdf.
- Bolton-Smith C, Price RJ, Fenton ST, Harrington DJ and Shearer MJ (2000). Compilation of a provisional UK database for the phylloquinone (vitamin K1) content of foods. *Br J Nutr.*, **83**: 389-399.
- Booth SL and Centurelli MA (1999). Vitamin K: A practical guide to the dietary management of patients on warfarin. *Nutr Rev.*, **57**: 288-296.
- Butler AC and Tait RC (1998). Restarting anticoagulation in prosthetic heart valve patients after intracranial haemorrhage: A 2-year follow-up. *Br J Haematol.*, **103**: 1064-1066.
- Crawley F, Bevan D and Wren D (2000). Management of intracranial bleeding associated with anticoagulation: Balancing the risk of further bleeding against thromboembolism from prosthetic heart valves. *J Neurol Neurosurg Psychiatry*, **69**: 396-398.
- D'Andrea G, D'Ambrosio RL, Di Perna P, Chetta M, Santacroce R, Brancaccio V, Grandone E and Margaglione M (2005). A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. *Blood*, **105**: 645-649.
- Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, Khatri P, Stettler B, Adeoye O, Moomaw CJ, Broderick JP and Woo D (2008). Warfarin use leads to larger intracerebral hematomas. *Neurology*, **71**: 1084-1089.
- Goz M, Goz F, Cakir O, Aydinol B and Eren N (2006). Warfarin resistance: Interaction between warfarin and *Eruca sativa* L. *Swiss Med Wkly.*, **136**: 327.
- Hadler MR and Shadbolt RS (1975). Novel 4-hydroxycoumarin anticoagulants active against resistant rats. *Nature*, **253**: 275-277.
- Hall BD (1989). Warfarin embryopathy and urinary tract anomalies: Possible new association. *Am J Med Genet.*, **34**: 292-293.
- Hall JG, Pauli RM and Wilson KM (1980). Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med.*, **68**: 122-140.
- Hanley JP (2004). Warfarin reversal. *J Clin Pathol.*, **57**: 1132-1139.
- Harrington DJ, Gorska R, Wheeler R, Davidson S, Murden S, Morse C, Shearer MJ and Mumford AD (2008). Pharmacodynamic resistance to warfarin is associated with nucleotide substitutions in VKORC1. *J Thromb Haemost.*, **6**: 1663-1670.
- Hou JW (2004). Fetal warfarin syndrome. *Chang Gung Med J.*, **27**: 691-695.
- Jensen KM (2008). What is the maximum safe dose of warfarin? <http://www.medscape.com/viewarticle/581599>.
- Kaminsky LS and Zhang ZI (1997). Human P450 metabolism of warfarin. *Pharmacol Therap.*, **73**: 67-74.
- Kim RB, Roden DM and Stein CM (2008). Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med.*, **358**: 999-1008.
- Lee PK, Wang RY, Chow JS, Cheung KL, Wong VC and Chan TK (1986). Combined use of warfarin and adjusted subcutaneous heparin during pregnancy in patients with an artificial heart valve. *J Am Coll Cardiol.*, **8**: 221-224.
- Leker RR and Abramsky O (1998). Early anticoagulation in patients with prosthetic heart valves and intracerebral hematoma. *Neurology*, **50**: 1489-1491.
- Osinbowale O, Al Malki M, Schade A and Bartholomew JR (2009). An algorithm for managing warfarin resistance. *Cleve Clin J Med.*, **76**: 724-730.
- Parvizi R, Makhdami N and Dinparasti R (2011). Warfarin resistance, a case report. *J Cardiovasc Thorac Res.*, **2**: 35-37.
- Phan TG, Koh M and Wijedicks EF (2000). Safety of discontinuation of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk. *Arch Neurol.*, **57**: 1710-1713.
- Qureshi GD, Reinders TP, Swint JJ and Slate MB (1981). Acquired warfarin resistance and weight reducing diet. *Arch Intern Med.*, **141**: 507-509.
- Routledge PA, Shetty HG, White JP and Collins P (1998). Case studies in therapeutics: Warfarin resistance and inefficacy in a man with recurrent thromboembolism, and anticoagulant-associated priapism. *Br J Clin Pharmacol.*, **46**: 343-346.
- Schwarz UI, Ritchie MD, Bradford Y, Li C, Dudek SM, Frye-Anderson A, Kim RB, Roden DM and Stein CM (2008). Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med.*, **358**: 999-1008.

- Sharma V, Biswas A and Saxena R (2007). Inherited warfarin resistance in Indian patients: Does it occur? *Clin Appl Thromb Hemost.*, **13**: 455-456.
- Sinxadi P and Blockman M (2008). Warfarin resistance. *Cardiovasc J Afr.*, **19**: 215-217.
- Song J, Li YQ and Fu WX (2007). A study of optimal INR value range of PT monitoring for oral anticoagulant after heart valve replacement. *Sichuan Med J.*, **28**: 270-271.
- Verstuyft C, Robert A, Morin S, Lorient MA, Flahault A, Beaune P, Funck-Brentano C, Jaillon P and Becquemont L (2003). Genetic and environmental risk factors for oral anticoagulant overdose. *Eur J Clin Pharmacol.*, **58**: 739-745.
- Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N and Cotrufo M (1999). Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol.*, **33**: 1637-1641.
- Wei W (2010). A Study on correlation between warfarin dosing and INR of anticoagulation therapy for patients with atrial fibrillation. Master degree thesis of Kunming Medical College. <http://cdmd.cnki.com.cn/Article/CDMD-10678-2010088601.htm>.
- Wijdicks EF, Schievink WI, Brown RD and Mullany CJ (1998). The dilemma of discontinuation of anticoagulation therapy for patients with intracranial hemorrhage and mechanical heart valves. *Neurosurgery*, **42**: 769-773.