Warfarin-induced skin necrosis

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Summary

Skin necrosis is a rare but serious side-effect of treatment with warfarin. At particular risk are those with various thrombophilic abnormalities, especially when warfarinisation is undertaken rapidly with large loading doses of warfarin. With the increasing number of patients anticoagulated as out-patients for thromboprophylaxis, we are concerned that the incidence of skin necrosis may increase. If skin necrosis does occur, prompt remedial action may be of benefit in preventing permanent tissue damage.

Keywords: warfarin; skin necrosis; protein C; antiphospholipid antibody; adverse drug reaction

Warfarin-induced skin necrosis (WISN) is an uncommon, catastrophic complication of oral anticoagulant therapy.¹ A substantial minority of cases occur in association with a familial deficiency of protein C² or protein S.³ An acquired deficiency of protein S secondary to the development of antiphospholipid antibodies has also been implicated.^{4,5} We present three cases of WISN, in two of whom antiphospholipid antibodies were the only identifiable predisposing factor. Neither of these two cases had a low protein C or S.

Case reports

Case 1

A 39-year-old woman with no personal or family history of thromboembolic disease suffered a deep vein thrombosis (DVT), confirmed by venography. Treatment was begun with intravenous unfractionated heparin which was continued for 2 days, after which she discharged herself from hospital.

One week later, she was re-admitted with clinical evidence of a pulmonary embolism. Intravenous unfractionated heparin was restarted and warfarin (two doses of 10 mg and one of 5 mg on three consecutive days) was commenced simultaneously. Heparin was discontinued on the third day, when the INR reached 2.3. That evening, she developed extremely painful ecchymotic lesions on both lower limbs. Initially, it was felt that these were haematomas, but over the next 12 hours it became clear that skin necrosis was developing. Despite re-heparinisation and treatment with fresh frozen plasma and intravenous vitamin K, she sustained extensive necrosis of the skin of both legs (figure). She was eventually discharged from hospital 3 months later, after skin

grafting. Testing for thrombophilia (table) revealed a lupus anticoagulant and high-titre IgG anticardiolipin antibodies.

Case 2

A 32-year-old woman had a history of venographically proven puerperal DVT, following which she was anticoagulated with warfarin for about 6 months without complication. Eight years later, she had a second pregnancy. Thromboprophylaxis with subcutaneous unfractionated heparin was begun immediately after delivery. One week later, she developed clinical evidence of a DVT and was warfarinised with simultaneous discontinuation of heparin. Three days after this, a painful 'bruise' appeared on her left thigh, which she had banged on a table. The skin in the centre of the affected area progressed to frank necrosis over the following 48 hours. Warfarin was discontinued, but no other treatment was given. Healing was slow and she required surgical debridement after 7 weeks.

One week after the debridement, she sustained a pulmonary embolism and received intravenous unfractionated heparin. After 48

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Figure Warfarin-induced skin necrosis affecting both legs

Table Investigations for thrombophilia. Cases 1 and 2 had evidence of lupus anticoagulant, as demonstrated by a prolonged dilute Russell's viper venom time (DRVVT) which corrected on the addition of platelet phospholipid (DRVVT(PN)). Case 1 had, in addition, raised IgG anticardiolipin antibodies and case 3 a reduction in free protein S. APCR = activated protein C resistance.

	Case 1	Case 2	Case 3	Normal range
Protein C (IU/ml)	0.96	1.00	1.37	0.67–1.38
Protein S antigen, total (IU/ml)	1.02	1.32	0.81	0.64–1.54
Protein S antigen, free (IU/ml)	0.71	1.34	0.55	0.61–1.43
Antithrombin (IU/ml)	0.89	1.02	0.92	0.80–1.20
Anticardiolipin IgG (g/l)	55.4	1.9	<5.0	<8.0
Anticardiolipin IgM (mg/l)	0	0.2	8.3	<11.0
DRVVT ratio	1.24	1.13	0.86	0.90–1.09
DRVVT(PN) ratio	1.12	1.03		
Kaolin clotting time ratio	0.8	1.04	1.03	<1.10
APCR	2.6	>3.6	not done	>2.0
Factor V Leiden	negative	negative	negative	negative

hours, warfarin was re-introduced (10 mg daily for 3 days and 5 mg on the fourth day). During the period of warfarinisation, her activated partial thromboplastin time remained within the therapeutic range. On the fourth day of warfarin therapy, when her INR was 5.2, she developed a well-circumscribed ecchymosis around the scar from her recent debridement and a similar lesion on her left calf. There was no history of trauma on this occasion. An ultrasound scan showed no haematoma. After 24 hours, the central area of the ecchymosis had become necrotic. Warfarin was discontinued. Over the next day, the extent of the necrotic skin did not increase and there was some improvement in the appearance of her leg. It was considered important to continue anticoagulation, and warfarin was cautiously reintroduced when the INR had fallen to 2.7, and was continued for 5 months. During this time, there was substantial healing of the affected areas, but a residual necrotic area eventually required surgical excision. Investigation revealed the presence of a lupus anticoagulant.

Case 3

A 26-year-old woman, with a history of pulmonary embolism on two occasions, was converted from warfarin to subcutaneous low molecular weight heparin and aspirin when she became pregnant. Investigations for thrombophilia had shown only a borderline deficiency of free protein S (table). She was delivered at 28 weeks' gestation by Caesarean section because of foetal distress. After delivery, heparin was continued and warfarin restarted. On the seventh postoperative day, when her INR was 3.1, she developed an area of extremely tender erythema on her left calf, surrounded by bruising. This was recognised as early skin necrosis and she was immediately treated with intravenous unfractionated heparin, vitamin K and fresh frozen plasma. Therapeutic heparinisation, initially with unfractionated, then with low molecular weight heparin was continued for two weeks, during which time her calf began to heal. Because of the strong history of venous thromboembolic disease, warfarin was re-introduced 15 days after the appearance of early necrosis. A daily dose of 3 mg was given with continuation of heparin until her INR was within the target

Learning points

- antiphospholipid antibodies can predispose to the development of WISN
- large swings in INR should be avoided during initiation of warfarin, especially in patients at risk of WISN and in those not receiving heparin
- early diagnosis and treatment of WISN lessens the risk of permanent tissue damage, and early WISN must be distinguished from haematoma formation

range. Eleven days after warfarin was restarted her INR was 3.8 and heparin was discontinued. Her calf healed with no permanent skin damage.

Discussion

When warfarin therapy is started, there is a more rapid fall in the concentration of protein C than of the other vitamin-K-dependent pro-coagulant factors. The temporary hypercoagulable state which results is believed to lead to the development of WISN in susceptible individuals. The use of large loading doses of warfarin may exacerbate this effect and may have contributed to the development of WISN in case 2. Particularly at risk are those with an inherited deficiency of protein C² or other impairment of the protein C pathway.^{6,7} There is *in vitro* evidence that an acquired deficiency of protein C or S may result from their inhibition by antiphospholipid antibodies.⁸ This might be a mechanism whereby antiphospholipid antibodies could predispose to WISN, although other mechanisms must also be operational to explain the occurrence of WISN without concomitant detectable protein C or S deficiency in our first two patients.

A consequence of the growth in the number of indications for warfarin therapy is that many patients are started on warfarin as out-patients. Protocols for the commencement of warfarin such as that of Fennerty *et al*⁹ aim to achieve a therapeutic INR within 3–4 days and were written for the treatment of acute thromboembolism, rather than for prophylaxis. We are concerned that such rapid warfarinisation in the out-patient setting without concomitant heparinisation may put some patients, such as those with undetected thrombophilic abnormalities, at risk of WISN. We agree with the suggestion¹⁰ that a more gradual approach, using low-dose warfarin and aiming to achieve a therapeutic INR in 10–12 days would lessen this risk without compromising the treatment of patients who are being electively anticoagulated. Patients known to be at risk of WISN (those with a previous episode, protein C or S deficiency and, our data suggest, antiphospholipid antibodies) should also be warfarinised in this gradual way, and consideration should be given in their case to therapeutic anticoagulation with heparin from the time of commencement of the warfarin until the achievement of an INR within the target range.

Our third case demonstrates that, if WISN does occur, prompt initiation of remedial therapy may prevent the development of permanent tissue damage. Initial appearances

may mimic those of a haematoma (a much more common complication of warfarin therapy) and a high index of suspicion is needed.

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Calcium-channel blockade can mask the diagnosis of Conn's syndrome

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Summary

A 30-year-old woman presented with hypertension and hypokalaemia, and was found to have primary aldosteronism due to a Conn's adenoma, whose removal cured the hypertension. Before surgery, the characteristic biochemical changes which enabled the diagnosis were completely masked by administration of a calcium-channel blocker, amlodipine. It is likely that widespread use of this class of drugs contributes to under-diagnosis of Conn's syndrome as a curable cause of hypertension.

Keywords: Conn's syndrome; aldosterone; calcium blockade

Figure Effects of treatment on plasma K^+ and aldosterone levels in a patient with Conn's syndrome. Plasma K^+ (—○—, left axis) and aldosterone (---□---, right axis) were measured before any treatment, and 4 weeks after the drug or surgical interventions shown on the x-axis.

Since its first recognition, the prevalence of primary hyperaldosteronism, or Conn's syndrome, as a cause of hypertension has been disputed. Initial optimism that 20% of hypertensives may have a curable cause gave way to a realisation that many patients with essential hypertension have low renin hypertension, and nowadays less than 1% of patients started on treatment for hypertension are considered to have the diagnosis. Recently, systematic surveys using a ratio of aldosterone to renin above 800 as an upper limit of normal have suggested prevalence figures greater than 10% (of hypertensives).¹ Ironically, changes in modern pharmacological treatment of hypertension have probably reduced the sensitivity of plasma electrolyte measurements for detection of Conn's syndrome, since the 4-8-fold lower doses of diuretics – and lower overall use of this class – than in Conn's time means that plasma K^+ values <3 mmol/l are seen infrequently; it is also likely that reductions in average salt intake limit the degree of hypokalaemia in Conn's syndrome. Both sodium and diuretic intake influence how much K^+ is lost through K^+/Na^+ exchange in the renal distal tubule. Angiotensin-converting enzyme (ACE) inhibitors suppress angiotensin-II-mediated aldosterone secretion. Suppression of aldosterone release from adrenal zona glomerulosa cells by Ca^{++} entry blockers is well described,^{2,3} but their effect in Conn's syndrome has been controversial.^{4,5} While the specific antagonist for aldosterone, spironolactone, is known sometimes to confuse diagnosis of an adenoma