Can small volume intramuscular injections be given to patients taking oral anticoagulants?

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Background

As increasing numbers of people are prescribed oral anticoagulants, for conditions such as atrial fibrillation, it is likely that a number will require a small volume intramuscular (IM) injection at some point. Factors that need to be considered in these cases include:

- Is there an increased risk of adverse effects, such as bruising or haematoma?
- Could the injection affect anticoagulant control?
- Could the anticoagulant alter the effectiveness of the injection e.g. vaccines?

This Medicines Q&A focuses on the potential risks of adverse effects associated with the administration of small volume IM injections to patients taking oral anticoagulants. Detailed analyses of drug interactions are outside the scope of this Q&A and further information should be sought on an individual patient basis.

Answer

Most of the published studies available on this subject relate to IM influenza vaccination in patients taking older anticoagulants, such as warfarin. Data are limited and some findings are contradictory. Over recent years there has been a wider uptake of the newer oral anticoagulants, apixaban, rivaroxaban, dabigatran and edoxaban, collectively named novel or direct oral anticoagulants (NOACs or DOACs), but there is very little published information about the risks of adverse effects with DOACs and IM injections.

Influenza vaccination

People taking oral anticoagulants commonly require vaccination against the influenza virus.

Studies of oral anticoagulants and intramuscular influenza vaccination

- A randomised, single-blinded trial (n=229) compared subcutaneous (SC) to IM influenza vaccine administered in the deltoid area in patients on oral anticoagulants (98% acenocoumarol, 2% warfarin) (1). Skin lesions (such as erythema) 24 hours after injection were reported by 37.4% of the SC group and 17.4% of the IM group (number needed to harm 5 [95% confidence interval 3.1 to 11.3]). No major side effects were reported. Two patients in the SC group and one in the IM group experienced a haematoma. No statistically significant differences were seen in international normalised ratio (INR) results between the groups.

- A randomised, double-blind, cross-over trial included 104 patients on stable warfarin therapy (2). Patients either received influenza vaccine or placebo into the deltoid muscle at the start of the first 28 day period and then, after a 14-day washout, crossed over to the alternative treatment and were followed-up for a further 28 days. Mean INR results, weekly warfarin dose and time in the therapeutic range were similar between the two groups in the two study periods. No major bleeding events were seen. Antibody response was not affected by warfarin treatment. The authors concluded that patients on stable doses of warfarin can safely be given influenza vaccine without the need to increase the frequency of INR testing.

- A study of 41 male patients taking warfarin assessed the effects of a 0.5mL influenza vaccine as a single IM injection in the deltoid region, followed by application of firm pressure for 5 minutes (3). All patients were followed up for 14 days and there were no cases of localised bleeding or any

change in arm girth after injection. Vaccination did not have a significant effect on prothrombin time.

- Thirteen male patients received 0.5mL influenza vaccine intramuscularly and 13 received the same vaccine subcutaneously in the deltoid region in a single-blind study (4). Three patients in each group had discomfort or pain at the injection site, but no local bleeding was recorded. Ten recipients of IM injection were followed up by phone 2 days later and no bleeding, bruising or swelling was described. The route of administration did not affect serum influenza antibody titres.

- A case-control study during the 2001-02 influenza season looked at the effect of influenza vaccination on prothrombin time in patients receiving long-term oral anticoagulant treatment (98% warfarin, 2% acenocoumarol) (5). Ninety patients [mean INR 2.79 (±0.83)] who received IM influenza vaccine were compared to 45 matched controls who did not receive vaccination. Influenza vaccination was associated with an average increase in INR of 0.56 seven to ten days after vaccination. Two patients experienced bleeding episodes (epistaxis and muscular haematoma). The authors suggest that INR should be monitored carefully in anticoagulated patients in the period immediately following influenza vaccination.

- A systematic review published in 2012 attempted to assess the validity of the assertion that the influenza vaccine may potentially interfere with the anticoagulant efficacy of long-term warfarin therapy (6). The review did not indicate any consistent, clinically relevant effect of influenza vaccine on INR results. The review also discussed that there does not appear to be an increased risk of haematoma following IM administration of the influenza vaccines.

Other information sources

A resource providing information and advice about drug interactions discusses that in small to medium studies (some uncontrolled), most did not demonstrate a significant change in prothrombin time or INR in patients taking **coumarins,** such as **warfarin** (7). Some studies found slight increases or decreases in anticoagulant effect, but these are probably of limited clinical relevance. However, in one large observational case-control study, an increase in INR from 2.64 to 3.85 was seen in about half of the 90 patients and 2 had bleeding episodes. The reasons for the difference between this study and others are not known. Overall, the weight of evidence suggests that the concurrent use of warfarin and influenza vaccination is usually safe and uneventful, but it would be prudent to be alert as there have been some reports of bleeding attributed to an interaction. **Acenocoumarol** does not normally interact with influenza vaccination.

An American reference source (AHFS Drug Information) also states that **influenza vaccine** may increase a patient's response to **coumarin-type anticoagulants** (8).

Practical Advice

Most seasonal influenza vaccines are licensed for both IM and deep subcutaneous (SC) use, but some prohibit SC administration (9). It has been suggested by one interaction resource that giving **influenza vaccine** to patients taking **warfarin** is normally safe, but that it may be preferable to give influenza vaccines by deep SC injection in patients taking coumarins and other anticoagulants due to the theoretical risk of haematoma (7). The summary of product characteristics for the influenza vaccine to be used should be checked to ensure that SC administration is licensed. If this is not the case, IM injection or an alternative preparation should be considered. There is no advice on this subject in the manufacturer's Summary of Product Characteristics (SPC) for the original brand of warfarin (Marevan®) (10).

The Public Health England "green book", Immunisation Against Infectious Disease, concludes that for influenza vaccines "there is a lack of evidence that the SC route of vaccination is any safer than the IM route in people taking anticoagulants" (11). It advises that individuals on stable anticoagulation therapy can receive IM vaccination. It also states that if there is any doubt, "to consult with the clinician responsible for prescribing or monitoring the individual's anticoagulant therapy".

Other vaccines

Limited information on the administration of vaccines to patients receiving oral anticoagulants is available. Individual SPCs should be consulted for further information. For example, the manufacturers of **yellow fever vaccine** (Stamaril®) recommend that due to the risk of injection site haematoma with IM injection, the vaccine should be administered via the SC route for patients taking an anticoagulant (12).

The results of influenza vaccination studies cannot be generalised to other vaccines or to IM injections with a higher volume or with needles of a greater calibre (1, 13). The risk-benefit ratio for persons at risk of adverse effects, such as bruising or haematoma, following IM injection must be evaluated by healthcare professionals.

Results from a retrospective cohort study in patients stabilised on **warfarin** suggest that no alteration in anticoagulant control would be expected after use of vaccines such as **23-valent pneumococcal polysaccharide vaccine** or **hepatitis A vaccine** (14).

A prospective cohort study analysed 28 children treated with warfarin receiving vaccines. There were a variety of vaccines administered including those from the routine schedule (DTaP-IPV, MMR, Hib etc.) and the influenza vaccine (87 total vaccine administrations). All children were within the expanded therapeutic range for their INR (within 0.2 on either side of the INR target). No unexpected variations in INRs were observed in this cohort. There were no muscle haematomas, clinically significant bruising or haemorrhagic events (15).

A letter to a journal details the results of a retrospective audit of 193 immunisations administered to children on long-term warfarin therapy at a single centre. 69.4% of the INR results pre-immunisation were in the therapeutic range but 10.4% were supra-therapeutic. There were no instances of major bleeding recorded within 48 hours after immunisation (16).

No data have been identified that show changes to antibody titres to other vaccines due to oral anticoagulants.

Direct/Novel oral anticoagulants

As discussed above, data on the safety of small volume IM drug administration to patients taking DOACs are very limited.

A study in Germany evaluated peri-interventional management of DOACs (rivaroxaban, dabigatran and apixaban) in unselected patients from daily care (17). Safety data was collected from a prospective registry of over two thousand patients taking a DOAC who also underwent interventional procedures that were classified as either ‘minimal’, ‘minor’ or ‘major’, based on severity of tissue trauma and the risk of peri-procedural bleeding. Intramuscular injections were classified as ***minor*** procedures which involved little tissue trauma but a ‘relevant bleeding risk’. To put this risk classification into perspective; procedures such as cataract surgery and pace-maker related surgeries were also deemed as ‘minor’ interventions. The authors concluded that due to the pharmacological profile of the DOACs (short half-life and fast onset of action) continuation or short-term interruption of a DOAC, without use of bridging therapy, is a safe strategy for most patients undergoing ***non –major*** invasive procedures, but advised that it would be prudent to conduct a careful risk: benefit evaluation before any patient specific decisions are made (17).

Expert opinion from a consultant haematologist supports this advice, suggesting that in clinical practice, if time allows, it is desirable to administer an IM injection 24 hours after previous DOAC dose and then to restart the DOAC the following day, assuming that there are no signs of haematoma or bruising. Although, in the opinion of the haematologist, short term interruption is unlikely to pose a high risk of a thrombotic event occurring, each patient’s individual circumstances needs to be carefully evaluated on a case-by-case basis (18).

The Summary of Product Characteristics (SPC) for dabigatran states that injection site haemorrhage occurs rarely (19). Application site bleeding is uncommonly reported in patients taking apixaban (20). Similar data are not included in the SPC for rivaroxaban (21) and edoxaban (22).

Other intramuscular drugs

Comprehensive information about the administration of individual IM drugs to patients receiving oral anticoagulants is beyond the scope of this Medicines Q&A. Individual SPCs should be consulted for further information. For example, some SPCs for IM drugs state that this route has not been evaluated in patients receiving anticoagulants because of the risk of haematoma. Therefore, the risk-benefit ratio for persons at risk of adverse effects, such as bruising or haematoma, following IM injection must be evaluated by healthcare professionals.

Actions when considering a small volume IM injection for a patient taking an oral anticoagulant:

- If possible, avoid IM injections, even when the INR is being closely controlled, and do not use if the INR is raised above the therapeutic range.
- Consider if alternative routes of administration are possible or if alternative drug therapy is appropriate.
- If small volume IM injections are necessary:
    - check the relevant SPC;
    - evaluate the risk-benefit ratio for each patient;
    - administer injections into an upper extremity as a precaution to permit easy access for manual compression, inspection of bleeding, and/or application of pressure bandages if necessary (10);
    - use a fine needle and apply firm pressure for at least 2 minutes immediately after vaccination (13)
    - Inform the patient that they should watch out for localised bleeding.

Summary

- Limited information is available on the administration of small volume intramuscular (IM) injections to patients taking oral anticoagulants, especially the newer Direct Oral Anticoagulants (DOACs). Most published studies relate to older anticoagulants, such as warfarin.
- IM injections should be avoided where possible, even when the INR is being closely controlled, and not used if the INR is raised above the therapeutic level.
- Healthcare professionals should weigh up the benefits and potential risks on an individual patient basis.
- An IM site on an upper extremity should be preferred to a central site, so that any bleeding can be seen, and compression applied if necessary.
- It has been suggested that deep SC injection of the seasonal influenza vaccine may be preferable if patients are taking coumarins or related anticoagulants, due to the theoretical risk of muscle haematoma.
- Not all influenza vaccines are licensed for SC administration, therefore the summary of product characteristics should be checked for each vaccine. If the vaccine is not licensed for SC administration, IM injection or an alternative preparation should be considered.
- Studies of influenza vaccination in patients taking oral anticoagulants have shown conflicting results. Some note that patients on stable doses of warfarin do not need to increase the frequency of INR testing, whereas some patients have experienced bleeding or haematoma.
- The Public Health England “green book” advises individuals on stable anticoagulation therapy can receive IM vaccination with influenza vaccines. The clinician responsible for the anticoagulation therapy should be consulted if there is any doubt.
- Currently, data on DOACs are very limited, although the manufacturers of some DOACs warn of the risk of injection site haematoma or haemorrhage.
- A single study from Germany suggests that continuation or short-term interruption of a DOAC, without use of bridging therapy, is possibly a safe strategy for most patients undergoing ***non – major*** invasive procedures, such as intramuscular injections. Conducting a careful risk:

benefit evaluation before any patient specific decisions are made is still a prudent course of action.

Limitations

- The information above is based upon limited published data
- The list of drugs is not comprehensive. Drugs which have not been included cannot be assumed to be safe when administered to patients taking oral anticoagulants.
- Detailed analyses of drug interactions are outside the scope of this Q&A and further information should be sought on an individual patient basis.
- Only the use of small volume IM injections has been considered. The use of other IM injections e.g. depot injections is beyond the scope of this Medicines Q&A.

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Search strategy
- Medline

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