Conclusion

Intermittent catheterisation is one of the major advances in urology. Users of the method are among the most satisfied and grateful of all patients.

For a free copy of the *User's Guide to Intermittent Catheterisation* please send a self addressed A5 envelope with 29p stamp to GMH at the address given above.

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Lesson of the Week

Insidiously evolving, occult drug interaction involving warfarin and amiodarone

B Cheung, F M Lam, C R Kumana

Interactions between warfarin and amiodarone may continue after amiodarone has been withdrawn, so more frequent monitoring of the international normalised ratio is advisable

Amiodarone is often prescribed in the treatment of supraventricular, junctional, and ventricular tachycardia, atrial fibrillation, and tachycardias associated with Wolff-Parkinson-White syndrome. Its advantages are its high degree of efficacy and the lack of negative inotropism. However, its use is complicated by its long half life, its side effects—for example, phototoxicity, skin discoloration, neuropathy, hepatitis, thyroid dysfunction, pulmonary fibrosis, and corneal microdeposits—and interactions with other drugs, including warfarin. The interaction between warfarin and amiodarone that results in prolongation of the prothrombin time and a risk of bleeding is well known,[1-3] and has been attributed to interference with the hepatic degradation of warfarin.[4] We report here a patient in whom this interaction was encountered in an apparently paradoxical manner.

Case report

A 72 year old man developed atrial fibrillation after coronary artery bypass graft surgery, and treatment with amiodarone (600 mg daily) was started. A fortnight later he had two transient ischaemic attacks. At that time, 18 days after starting amiodarone, the dose of amiodarone was reduced to 400 mg/day and anticoagulation with warfarin was started. When the patient's prothrombin time appeared to have stabilised (table) he was discharged from hospital taking warfarin 2 mg and 2·5 mg on alternate days. Eighteen days later he was admitted to hospital with gross haematuria and an international normalised ratio of 4·7. Following transfusion of fresh frozen plasma and withdrawal of warfarin, the international normalised ratio became normal. Investigation of the urinary tract, including cystoscopy, showed no abnormality. Between the beginning of warfarin treatment and admission to hospital for haematuria no new drugs were started and nor was the dose of any other drug changed.

Discussion

Amiodarone is a very lipid soluble drug with complex pharmacokinetics.[5] It is metabolised by the

International normalised ratio and dose of warfarin after start of warfarin

Days after start of warfarin	Dose of warfarin (mg)	International normalised ratio
1	2·5	1·2
2	3	1·5
3	2·5	1·7
4	3	2·0
5	2·5	2·2
6 and thereafter	2 and 2·5 on alternate days	
18 (presented with haematuria)		4·7 and later 4·2

Division of Clinical Pharmacology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong
B Cheung, *lecturer*
F M Lam, *medical officer*
C R Kumana, *professor*

Correspondence to:
Dr Cheung.

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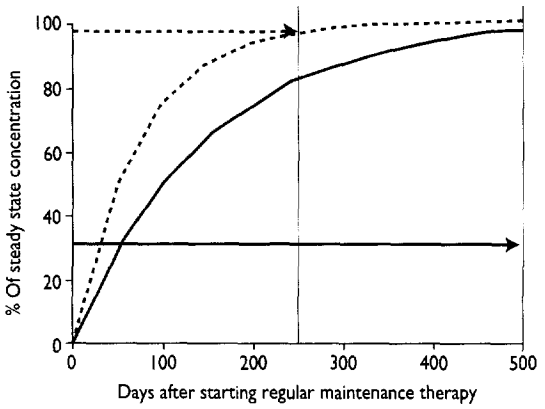
liver and accumulates in tissues, especially adipose tissues and the lungs. Its elimination half life is long (13 to 107 days) and its volume of distribution has been reported to be 0·9 to 148 l/kg. Consequently, it may take many months (or even over a year) for patients receiving regular maintenance treatment to achieve a steady state. Although our patient achieved what appeared to be satisfactorily controlled treatment with warfarin (as assessed by international normalised ratio monitoring), this was only 23 days after starting treatment with amiodarone, at which time it was unlikely that the latter had attained a steady state. With regular maintenance dosing, the drug must have continued to accumulate, eventually causing a symptomatic interaction with warfarin.

Other evidence has shown that amiodarone treatment results in gradually evolving effects, consistent with slowly accumulating tissue concentrations, and that such effects persist for considerable periods after stopping treatment.[6] Thus, the majority of its side effects, which are largely dose dependent (type A), usually become clinically manifest weeks or months after starting treatment. Similarly, on stopping amiodarone, they often take weeks or months to resolve (consistent with very gradual drug loss from the tissues). Furthermore, in the event of adverse effects developing during successful long term amiodarone treatment, physicians often prescribe "drug holidays" without apparent loss of antiarrhythmic efficacy.

Amiodarone, an increasingly popular antiarrhythmic agent, may also give rise to clinically significant interactions with other cardioactive drugs, such as digoxin, quinidine, and procainamide.[7] Those starting to take these other drugs days, weeks, or even months after starting amiodarone, may nevertheless be subject to a gradually evolving drug interaction. Any resulting toxicity might appear after a period of apparently well controlled initial treatment and the causative drug interaction may go unrecognised, especially when no new treatment has been started. This interaction may also be clinically relevant during withdrawal from long term amiodarone treatment. For example, in patients taking warfarin discontinuation of amiodarone can be expected to result in a gradual decrease in the international normalised ratio over the ensuing weeks or months.

In the context of this drug interaction, it should be noted that during established treatment with amiodarone the dosage of warfarin has been reported to be about 16-45% of the usual dose.[1] Secondly, international normalised ratio values within the therapeutic range may not remain so if the tissue amiodarone concentration has not attained a steady state (figure). We recommend that in patients who have started amiodarone within the past few months (and possibly up to a year earlier) anticoagulation with warfarin should be undertaken carefully, lest the ensuing drug interaction results in insidiously increasing international normalised ratio values and excessive anticoagulation. It may be prudent to double the frequency for monitoring prothrombin times, and modify the frequency accordingly once the values become more stable. The same recommendations may apply whenever long term amiodarone treatment is to be discontinued while warfarin is continued.



Relation between amiodarone concentration (expressed as a percentage of steady state concentration) and duration of regular maintenance therapy when its elimination half life is 50 (---) or 100 (——) days. Time to steady state concentration is depicted by arrows, indicating the theoretical windows during which the warfarin dosage requirement may change. This figure assumes that tissue amiodarone concentration conforms to first order pharmacokinetics and that after the start of regular maintenance therapy, steady state concentrations are virtually achieved after a period corresponding to five elimination half lives

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ANY QUESTIONS

What are the relative incidences of anaphylactic reactions to the first, second, and subsequent doses of intravenous drugs? Is there any logic in medical staff being required to give first drugs and nursing staff being happy to give the second and subsequent doses?

An anaphylatic reaction during a course of drug treatment is rare but if a person has antibodies to a drug anaphylaxis is more likely to occur on first exposure to it. In the classic description of anaphylaxis a latent period of two weeks is required for the generation of specific antibodies to a compound. Development of anaphylaxis is therefore unlikely during a course.

In 530 patients who developed anaphylaxis after intravenous drugs in the perioperative period we have seen two who apparently reacted after an uneventful first exposure to the same anaesthetic and one who reacted after one and a half hours of infusion.

There are other non-allergic effects, often related to the dose, associated with the administration of intravenous drugs that may be more apparent at first injection, but I know of no data to support this.

Anaphylaxis occurs in three in 10 000 patients in hospital.[1] The logic of having a doctor present at the first injection is supported by the likelihood of a reaction but should be considered in the light of the low risk and the time that it would take a doctor to respond to an emergency call.—MALCOLM FISHERS, *head, intensive therapy unit, Royal North Shore Hospital, St Leonards, New South Wales, Australia*

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