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Warfarin self-dosing, a case study on long term self-management of anticoagulation

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Abstract

Background. We know very little about the patients who self-manage warfarin dosing. There has been little published on self-managing anticoagulation, with Ward et al[1] being a recent exception. Any active patient should learn to self-manage their health. But how do they do it? How do they reason? This knowledge is essential if the health profession seeks to train patients and reduce the burden on healthcare needs. This case study is based on 24 years data on self-managing anticoagulation.

Methods. In other fields such as child development and linguistics, detailed case studies have significantly advanced our knowledge.[2] In particular they have provided a source of hypotheses which can be tested and refined in cross sectional or experimental studies. Data from reliable self-dosers is an under-used resource to support self-management of warfarin.

Main finding 1. The patient has found that his background biological variation is >2 INR, which if validated would necessitate major changes to current common dosing algorithms based on an expected ≤1 INR.

Main finding 2. The patient has also refined the two step algorithm for dosing proposed by Kim et al[3], first by adding the method of stepping. Second, he has prioritised the reasons for an extreme INR as: 1/ chance, 2/ change in level, 3/ change in the input=output balance. His refinements enable the reason for the extreme INR to be established, and this reason guides the dosing decisions.

Conclusions. Self-dosers need more information about swings. Research is needed to compare stepping and kicking, and each long term patient needs to experiment in order to know how these methods work for them. The use of oral Vitamin K as an alternative to kicking needs investigation. Finally, a mechanism needs to be set up for tapping and publishing the resources and know-how of skilled patients as a potentially rich source of hypotheses and medical practice.

Keywords:
Warfarin, self-management, self-monitoring, self-dosing

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Case history

In September 1993, a 35-year-old male had his mitral valve replaced with a St Jude valve at Cardiff University Hospital. In January 1994 he went abroad to work. He has been self-dosing since release from hospital. As an expatriate he reports the need to take medical decisions and has grown in confidence helped by his scientific background in Human Biology. His wife is a nurse and he discusses decisions with her, though he has the final decision. He can quote research showing that in Cystic Fibrosis patients do better when there is a significant other person who checks on them regularly.[4] Any discussion about self-dosing needs to include this vital element.

Before leaving hospital, he asked a cardiologist in Cardiff about how to adjust the dosing and was told that it was easy: it was just like charging a paintbrush, and the half-life of warfarin was a variable two days, therefore dosing had a time lag. Health information leaflets warned him of some drug interactions. He purchased the British National Formulary which he rates highly though regrets that the half-life of drugs is rarely stated. Over the years he reports having built up his knowledge from the occasional remark from doctors and cardiologists in the UK and abroad, through his own reading of the health literature and, crucially, through his own reflections which have been enhanced by having to cope with several difficult times without help from a health care professional. His target range was set at 2.5 to 3.5 by his surgeon though other cardiologists later told him that 3 to 4.5 was probably wiser.

Images

Images are a powerful conceptual framework. We simply do not know what images self-dosers have, and which ones are the most useful. The charged paintbrush image needed no further explanation since DIY was his hobby. His preferred image nowadays is the reservoir, with variable heights representing the changing INR. This reservoir is constantly losing warfarin, which is topped up daily. Because the reservoir contains a buffered liquid (GCSE school chemistry concept) it does not matter that the dosing happens once per day. He also likes the image of the loose steering wheel to explain dosage correction: if you make a small change nothing happens, but when you change even more, then it jerks too far the other way. Sailors face a similar problem with sluggish boats, and techniques sailors use could be applicable to dosing.

Precision, reliability and validity of the test instrument

All scientists need to know the precision of their measurements. That was one of the life-long take-home messages from his Physics 'A' level. He knows that there are differences between labs, and within labs. Abroad he can easily get the INR checked cheaply at any laboratory. Seeking to enhance reliability, he asked a local doctor to recommend a good lab and used it until in 2013. A British doctor persuaded him to buy the Coaguchek meter, mainly for travelling in Europe where testing is difficult and expensive, and also to improve the reliability and validity of his testing. It is probably better because of reliability issues to stick to self-testing all the time.

He searched the medical literature and knows that Coaguchek and the laboratory often differ, and that the validity of any results has a margin of 0.5 INR. In addition, he does not know if this MoE (margin of error) is higher for the low INR which concerns him most. The clear implication is that we must allow for the 0.5 in the dosing algorithms.

The patient is now aware that the minimum level of protection starts when the INR=2 and wishes he had known this right at the beginning. He now reasons that when combined with the MoE of the tests, the lowest acceptable INR is 2.5 and not 2.0.

The background size of the INR

Long term dosing success is often evaluated by looking at how often a patient is able to stay within range, and most ranges are set at 1.0 INR. Many health practitioners, and patients, know that this range is arbitrary and small.
What is interesting is that if I fell out of range it took the system at least two or three go's to get me back due to yo yo effect, whereas if I ignored what they said and carried on with the dose I have always taken it returned much quicker.
April 23, 2016, Bob W Healthunlocked

It is a fundamental point of human biology that unless you know the natural range you have no means of knowing if your target range is realistic. Data from self-dosers who are self-managing their condition is a unique untapped resource which can be used to discover this natural range. This patient reports being very relaxed about the INR, and he is happy to be able to act upon what he believes, without fear of legal constraints and without arguing with a doctor. He has kept records for 24 years. Here is some example data, with my comments.

Table 1. Example data with comments

18/02/2009	3.78	
13/03	4.6	Too high, but there was no dosage correction, there was regression towards the mean
24/03	3.18	
30/04	3.53	
13/06	2.33	Too low, but there was regression towards the mean
16/06	3.38	
-----		Conclusion. Natural range 2.33 to 4.6

26/06/2003	2.4	All three readings on the same dosage
02.07	2.8	
14/07	4.8	

02/06/2006	3.1	
21/07	2.8	
15/09	3.8	
20/10	2.8	
29/12	3.3	
13/03/2007	2.5	Notice the jump from one extreme to the other, all without changing the dosage
30/03	4.48	

06/04	3.5	
15/06	4.53	
27/06	3.3	
14/09	5.54	Missed one day then normal dosage
05/10	3.7	No dose correction

Table 2. Summary table of ranges experienced over 24 years

Minimum to Maximum INR	Range
2.33 to 4.66	2.33
1.8 to 3.85	2.05
2.4 to 4.8	2.4
2.5 to 4.48	2.18
2.24 to 4.6	2.34
1.8 to 4.11	2.31

The natural background rate in Table 2 is as high as 2.4. For this patient therefore, he thinks an enforced range of 1.0 would be absurd. He believes that premature correction also has the effect of making the swings worse, which increases the chances of a brain haemorrhage or a blood clot. He asks the question as to how many patients have seriously suffered because enforcement of a narrow range has caused dangerous swings.

The dreaded swings in INR

The patient is more concerned to avoid swings than he is to avoid a high INR. He likes to explain it by inviting people to do a simple thought experiment. Assuming the normal dose is 5mg and the target range is the very narrow 2.5 to 3.5. One day the INR=2.2. His personal guidelines say that two or three out of range results are needed to ensure this is a real change needing correction. If he prematurely increases the dosage by a half mg, he could get a swing to an INR of 5+, necessitating missing a day then restarting at the old dosage of 5mg. Then, because the system is now swinging wildly, the next result could easily be 2.0 and he has created wide swings which are difficult to stabilise.

The patient is frustrated by the lack of easily available data to help him with dosing decisions. He would like to know more about swings. So, for instance, when he sees a result of 3.8, then 4.5, how soon is it likely to peak? At what level? This implies, how long does he leave it before he tests again? Testing too soon could mean a premature attempt to correct the dose.

Balance of probability: INR preference

The patient reasons that a low INR means a high probability of a clot, and the consequences are almost always serious. A high INR only has a risk once the bleeding starts. Bleeding in the brain is serious and the rest usually are not. With this reasoning, combined with the MoE of 0.5, the patient has decided in future to act quickly to correct a low INR of less than 2.5, and the fact that his natural range is >2 means he chooses to tolerate higher INRs.

The INR curve

The patient relies on simple GCSE level statistics. He knows that the dosage-INR curve is not linear and is not symmetrical. He understands that lower INRs are easier to manage than higher INRs, which feels counter-intuitive if you rely on a simple linear relationship. He knows that while higher INRs are created by higher doses, small dose changes have greater effect. So, when his INR is too low, he makes a dose change of plus 0.5mg. But, when his INR is high, he changes the dose by minus 0.25mg. He wonders how many clinicians may know and practice this.

Correcting a high INR

A standard method is to miss a day or more. The patient does not know what exactly happens when you miss a day. He expects variation[5] and as someone who lectures on child development, he knows that individual variation is likely to be high, but he would still like to know the mean and 95% confidence intervals of missing a day for various starting points. Now that he has his own INR monitor he intends to find out by conducting two self-experiments: missing a day when the INR is high and missing one day when the INR is low, by checking his INR daily for a week. All he knows is that when he had 5.54 and missed a day, and resumed without changing the dosage, this resulted three weeks later in a 'healthy' level of 3.7. He reports that when he had 5.7, he chose to miss one day, and the INR was 5.18 the next day and presumably still falling, so he resumed normal dosing, and he was right. In short, he did NOT follow the standard advice to wait until the INR was below 4 before restarting the warfarin, and he certainly did NOT restart at a lower dosage because input would not have been sufficient to maintain the level, and the INR would have become unacceptably low.

It is interesting that one study found it is safe to continue without a dose change and advises a repeat test "in about 2 weeks".[6] Therefore, the idea that you wait until you are in range before restarting warfarin could be widely off the mark. Stopping warfarin for two or more days risks two dangerous consequences: an extremely low INR a few days later, and the dreaded swings.

The patient knows there are at least six ways, which can be combined, of correcting a high INR.

1. Do nothing, and rely on regression towards the mean
2. Miss one or more days to reduce the INR
3. Stepping
4. Kicking
5. Take a Vitamin K supplement of 1-2.5mg with or without missing a day
6. A small dose reduction: use of 0.25mg

If there is no immediate danger, the patient first tries option 1: do nothing, then options 3 or 4, stepping or kicking only. He finds it strange that these methods are not widely acknowledged. Only if these fail does he resort to stepping or kicking, followed by a small

dose change. This is because he thinks there are three reasons for an unusual INR, prioritised as follows:

1. Chance
2. Change in the reservoir, adjusted by stepping or kicking
3. Genuine small change in the maintenance dose

On the other hand, he also knows that the easiest way to boost a low INR is to (semi) fast for 1-2 days.

Stepping

Imagine the target range is 2.5 to 3.5. The steady usual dose is 5mg. One month ago, the result was 3.0, and now it is 4.0. In some algorithms this would mean an immediate dose decrease of 10-20%. But decreasing the maintenance dose assumes that the dosage of warfarin to maintain input=output has changed and takes no account of the other major variable: the reservoir level. The patient reasons that since a **change in the reservoir level is far more likely than a change in the input = output equation, a modification of the reservoir level needs to be tried first**. It is done by dosing 4, 4, 4.5, and 5 which creates a gentle swing, and also reduces the level in the reservoir. The common advice to miss a day would bring the INR down but risks swinging to <2. Stepping follows the maxim to make dose changes gently. Stepping to correct a low INR, could be 6.0, 5.5, 5.0 on the assumption that the level in the reservoir needed topping up without changing the regular dosage. **Stepping is gentle, and has the important role of helping the doser to distinguish between when a genuine dosage change is needed and when a simple adjustment in the height of the reservoir is enough.**

Kicking

Kicking is when you do something drastic for one day then carry on as normal. Missing a day is a form of kicking. Given that warfarin is an inherently sluggish system, the logic is that kicking should be more useful than stepping.

Table 3: Stepping and kicking for high INR

Example. 5mg daily dose. INR suddenly is 6.0	
Stepping	Kicking
4, 4, 4, 4.5, 5	Miss a day, 5mg

Table 4: Stepping and kicking for low INR

Example, 5mg daily dose. INR suddenly is 1.8	
Stepping	Kicking
6, 6, 6, 5.5, 5	8, 5

The analogy of steering a sailing boat makes testable predictions and suggests that kicking may be more effective than stepping, even though there is a greater risk of creating swings. That is an easily testable hypothesis.

Just before this article was ready for submission, the patient reported that he had the chance to do a head for head comparison of Option 2, missing a day, and Option 3, stepping. He had a high INR under similar circumstances to two years ago, when he had used Option 2. So,

this time he used Option 3. This is anecdotal evidence that the two are similar: 75% dose then 75% dose then the new dose, is equivalent to 0% then new dose.

Table 5: Kicking (Miss a day) versus Stepping

Kicking -- Miss a day		
Date	**INR**	**Subsequent dose**
15.05.15	4.0	4mg
26.05.15	5.7	Miss a day, then 3.75mg
03.06.15	3.5	

Stepping		
Date	**INR**	**Subsequent dose**
15.04.17	3.3	4mg
08.05.17	4.8	3, 3, then 3.75mg
13.05.17	3.0	

Use of 0.25mg

The patient used to think that 0.25mg was impossibly small. However, breakable half mg tablets are now available, and he has found from experience he can break the 3mg and 5mg into quarters and maintain a tight range over many months. He also used to think that the 0.25mg would be dwarfed by diet. This patient reports that he has a very irregular diet, with variable content and meal times. He has found use of 0.25mg to be incredibly useful, and they are much better than alternate days of 5.0/5.5, particularly when a 40% reduction was made, due to a course of Amiodarone which necessitated a dose of 3.75mg.

When there is an obvious cause, for instance the commencement of Amiodarone, he reports that he takes prompt action and does not wait to see if an unusual result is due to chance. He then likes to run the dosing so that there is margin. For instance, he knows that Amiodarone takes months to phase out of the system. Instead of testing weekly, he chose to keep the INR relatively high, knowing the tendency to become lower. He also correctly predicted that for a while at the end of coming off Amiodarone the INR would be higher for a few months. His prediction was based on his hospital experience of the Heparin bridge and his discovery that the new stable dose is not necessarily the same as the old stable dose.

Frequency of testing

The patient is aware that there is a time lag for a swing to reach its peak and regress, a time lag whose likely duration is not known but is thought to be 1-8 weeks. He knows that the use of more frequent monitoring increases the tendency to needlessly and unhelpfully intervene. He can cite as comparable evidence the warning against too frequent monitoring of thyroid levels on coming off Amiodarone[7] (the warfarin dosing for initiation and termination he successful handled himself). Just as there is the need to recognise that the thyroid gland will sort this out naturally, without intervention, more frequent monitoring requires with it the courage to watch, to wait and see, and do nothing.

Pulling together the threads: (a practical approach to self-managing INR as learned over 24 years)

Given the MoE and his natural range, the patient has decided that his goal is 2.5 to 4.5 with a preference for >3.0. With a result of <2.5 he is likely to intervene promptly rather than wait for regression to the mean or to try to distinguish between chance or the genuine need for a

dose change. With a result of >4.5 he is likely to act much slower. He worked all this out for himself and was quite chuffed when he discovered similar reasoning in the framework of Kim et al.[3] Because he cannot find relevant research he intends to track the INR for himself next time he chooses to miss a dose. He would also like next time his INR is >5 to track the effect of 1mg of Vitamin K, and at the other extreme to see how well semi-fasting works to boost the INR.

First aid in the event of risk of bleeding

The patient is aware that his tolerance and preference for higher INR goes against conventional advice, which he has seen move over the decades towards a lower INR. He has also seen the growing interest in oral Vitamin K tablets. In the days when Vitamin K was not available in small doses, he ordered from Amazon some 100mcg tablets, knowing that in an emergency he could take orally 10 tablets equivalent to 1mg. He knows that in even minor accidents that could cause a brain haemorrhage, then a low INR would be a big help. Taking the oral Vitamin K before reaching hospital would gain time. Therefore, he carries 100mcg tablets and intends to take ten of them routinely at every incident such as a bang on the head, and deal with the INR later. He also knows about the newer dressings such as Alginate which aid coagulation, and he has invested in portable 2g sachets of Celox, a haemostatic powder.

Pitfalls in the standard advice on dosing and INR

When asked how he viewed the standard advice he reports to being nervous, as his medics may want to impose advice that he thinks could be wrong. He is concerned about:

1. An insistence on seeking a range which is significantly narrower than the natural range
2. Too quick a use of dose changes for out of range results instead of stepping
3. The only mechanisms of correction are dose change, and the drastic step of missing one or more doses
4. There is little appreciation that a low INR requires prompter action than a high INR.

Conclusions

It can no longer be assumed that the natural range is less than one. Therefore, wider ranges should be accepted, and dose change should be rarer. Research is needed to accurately describe this natural range. A range can only be set with confidence once the natural range is known; otherwise there will be striving for too artificially narrow ranges.

The paper has highlighted the lack of accurate information available to a self-doser concerning the properties of swings in INR and the different and probably better ways of managing them. A clear prioritised list of likely reasons applicable to all warfarin patients with an out of range result has been presented and linked with dosing methods.

More sophisticated methods such as stepping or kicking need investigating to be considered into the decision-making algorithm.

The author realises the limitation of this paper in that the data is only from one patient and may not be reproduced reliably in another patient for reasons related to pharmacokinetic and pharmacodynamic variability. The effect of stepping and the effect of kicking are probably different in everyone. In turn this highlights the need for systematic experiment for each patient on long term warfarin and that this knowledge of their own case be included in the decision-making process.

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