The Clinical Effect of Atovaquone/Proguanil on Warfarin Therapy in Adults

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Background

Warfarin therapy is a vitamin K antagonist that has been used for decades as an effective oral anticoagulant. However, it is also well-known that it interacts with many different drugs which can lead to changes in the patient's International Normalized Ratio (INR). Atovaquone/proguanil is one of these potential interactions. Tertiary references suggest an interaction but there is no specific literature regarding atovaquone/proguanil in combination or in doses used for malaria prophylaxis. The local Anticoagulation Clinic had a warfarin monitoring guideline specific for patients who are prescribed atovaquone/proguanil. The guideline advised to have the patient take atovaquone/proguanil for a 4 day trial while on warfarin and to monitor INR on day 4 to assess for any changes in INR. Clinicians in the Anticoagulation Clinic began to question if this monitoring strategy was necessary as little or no drug-drug interaction was noted anecdotally.

Objectives

The purpose of this study is to evaluate if there is a clinically significant interaction between atovaquone/proguanil at doses used for malaria prophylaxis with warfarin.

Methods

This descriptive study involved retrospective chart reviews of all patients from March 2009 to October 2014 who picked up an atovaquone/proguanil prescription from a Kaiser Permanente San Jose Outpatient Pharmacy while concomitantly taking warfarin as directed by the San Jose Anticoagulation Clinic.

The following data were included in the analysis:

- warfarin and atovaquone/proguanil indication
- atovaquone/proguanil dose and duration
- Time in Therapeutic Range (TTR) for 1 year prior to patient's atovaquone/proguanil prescription or since date of warfarin initiation
- INRs prior, during and after completion of atovaquone/proguanil therapy

Each case was also evaluated for any warfarin adverse events including any minor or major bleeding as well as other possible confounding factors.

Disclosure

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Results

Table 1. Baseline Demographics (n=27)

Age	Average: 68.1 years Median: 71 years
Sex	78% male (n=21)
Warfarin Indication	Atrial fibrillation alone - 82% (n=22) VTE (recurrent or single) - 11% (n=3) Aortic Mechanical valve replacement -3.7% (n=1) Vascular occlusion - 3.7% (n=1)
TTR	Average: 71% Median: 69.1%

Table 2. Pre-trip analysis

	% (N)	% of therapeutic INRs (N)	% of elevated INRs (N)	% of low INRs (N)	TTR	Average % decrease in dose
Warfarin dose reduced while on study medication	29 (7)	0 (0)	71 (5)	28.6 (2)	62.2%	7.1%
Warfarin dose unchanged while on study medication	71 (17)	88 (15)	0 (0)	12 (2)	76.5%	N/A

Table 3. Post-trip analysis (INRs drawn while still on atovaquone/proguanil)

	% (N)	% of therapeutic INRs (N)	% of elevated INRs (N)	% of low INRs (N)	TTR
Warfarin dose reduced while on study medication	35 (6)	50% (3)	17 (1)	33 (2)	63.3%
Warfarin dose unchanged while on study medication	65 (12)	67% (8)	25 (3)	8 (1)	69.3%

Table 4. Post-trip analysis (INR drawn off atovaquone/proguanil for at least 7 days)

	% (N)	% of therapeutic INRs (N)	% of elevated INRs (N)	% of low INRs (N)	TTR
Warfarin dose reduced while on study medication	28 (7)	71% (5)	14 (1)	14 (1)	62.2%
Warfarin dose unchanged while on study medication	72 (18)	83% (15)	11 (2)	6 (1)	76.5%

References

Hidalgo K, Lyles A, Dean SR, "A Potential Interaction between Warfarin and Atovaquone," Ann Pharmacother, 2011, 45(1):e3.
Armstrong G, Beg MF, Scahill S, "Warfarin potentiated by proguanil". Br Med J 1991; 303:789
Rosendaal (TTR) calculator - https://www.inrpro.com/rosendaal.asp (last accessed 7/9/15)

Discussion

- There were no emergency room visits related to anticoagulation during the study period.
- A critical INR occurred during the post trip period. However, the patient never returned back to the warfarin dose that he was on prior to taking atovaquone/proguanil which suggests that the elevated INR was unrelated to atovaquone/proguanil.
- There were a total of 27 cases included in our review, but not all were included in all our analyses.
  - Three patient cases were excluded from the pre-trip analysis as it was not clear if these patients completed an atovaquone/proguanil trial prior to the trip start with subsequent INR 3-4 days after starting medication.
  - One patient was excluded from the post-trip analysis since warfarin was discontinued during the trip and, therefore, no follow-up was done.
  - One patient's warfarin was adjusted by a physician during the trip and, therefore, was excluded from our analyses.
- For the majority of patients, warfarin was not adjusted in anticipation of travel since there was no noted effect on INR after trial.
- In those patients whose warfarin doses were reduced (presumably due to the drug-drug interaction), a handful of patients actually had elevated INRs and a small number (two) had subtherapeutic INRs. While this may suggest that a small subset of patients may actually have a drug-drug interaction, it is important to note that the TTR was much lower in this population (62.2% vs 76.5%).
- For the post trip analysis, regardless of whether a patient's warfarin dose was reduced or not in anticipation of a drug interaction, there were still a handful of patients in each group who became subtherapeutic or supratherapeutic.
- For patients who were out of range while still on atovaquone/proguanil, only one patient required resumption of his/per previous weekly dose. All others needed a one time dose change and then they resumed the same weekly dose that they were on during the trip. This suggests that the low or high INR was likely not due to atovaquone/proguanil but simply diet/activity changes during trip.

Limitations

- Small sample size
- Single center
- Lack of diversity among patients
- Limited data sets
- Adherence to atovaquone/proguanil was not measured throughout study
- Uncontrolled

Conclusion

Through this limited data set we conclude that there is likely (though not definitive) no significant drug-drug interaction at doses used for malaria prophylaxis. We do not feel that empiric warfarin dose adjustments are needed when patients are prescribed atovaquone-proguanil at doses for malaria prophylaxis. Moreover, there is no need to "test" the patient for potential drug interaction prior to travel.