International normalized ratio increase in patients taking oral anticoagulant therapy and using sildenafil (viagra®)

We report two cases of increased hypocoagulability in patients taking warfarin and acenocoumarol.Two white men, aged 68 and 65 years, on long-life oral anticoagulation, one with warfarin and another with acenocoumarol, used sildenafil concurrently. In both cases the International Normalid Ratio (INR) increased, much more in the patient taking acenocoumarol. Sildenafil is used for the treatment of erectile dysfunction. It has high plasma protein binding and hepatic metabolism, being a weak inhibitor of cytochrome P450 CYP 2C9. Its use concurrently with oral anticoagulants can cause a bleeding risk as consequence of increasing INR. In the first case the risk was minimized by splitting the daily a acenocoumarol dosage; in the second case, the patient himself decided not to stop ranitidine when he takes sildenafil. Patients taking acenocoumarol or warfarin must be informed about a posible risk of bleeding if they use sildenafil concurrently.

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Introduction

The widespread use of sildenafil for the treatment of erectile dysfunction in men has also led to its use in patients on oral anticoagulant treatment (OAT) in spite of the secondary effects and contraindications. It is known that sildenafil is a phosphodiesterase inhibitor with rapid absorption, and its half-life increases when it is administered with food or grapefruit juice.[1] It has high plasma protein binding from 93 to 96%[2,3] and hepatic metabolism through the CYP 3A4 (major route) and the CYP 2C9 (minor route) microsomal isoenzymes.[2] Its clearance was decreased in healthy volunteers 65 years of age or older, with free plasma concentrations approximately 40% higher than those measured in healthy younger volunteers, as well as in volunteers with severe renal impairment and with hepatic cirrhosis.[4] Precautions for its use are bleeding disorders or active peptic ulceration, coronary ischemia or congestive heart failure and A multi-drug antihypertensive regimen. Taking into account the sildenafil information,[2] no significant interaction was noted when warfarin 40 mg was given with sildenafil because it is a weak inhibitor of cytochrome P450 2C9 enzymes, which partly , metaboliz a warfarin and acenocoumarol.

We report the cases of two patients on OAT using sildenafil whose International Normalized Ratio (INR) values increased.

Case reports

Case 1. A 68-year old man with a mechanical aortic heart valve prosthesis taking OAT since 1984 also had chronic hepatitis since 1985 and only one functioning kidney. He is taking enalapril as an antihypertensive drug and acenocoumarol in one daily dose as anticoagulant. His therapeutic range (TR) for anticoagulation is an INR between 3 to 4. After using sildenafil, his INR increased from 3.05 to 7.7 without bleeding complications. The coumarin derivative was stopped for 24 hours (hrs) and the dose was lowered to 3 mgt weekly. The patient decided to continue taking sildenafil once a week. Our decision was to split the daily dosage of acenocoumarol into two parts taken every twelve hrs to minimize the effects sildenafil. The last four INR measurements (INRs), made every five weeks, were in the TR (3.01, 3.13, 3.08 and 3.12).

Case 2. A 65-year old man with mitral valve heart disease suffered a stroke three months before the facts described here. He was on OAT with warfarin since June 2002 and he maintained a TR between 2.5 to 3.5. He was taking ranitidine as a gastric protector and pravastatin to decrease colesterol levels. He used sildenafil once a week, and on that day did not take ranitidine. The first three times (Table 1) the INR increased, and suffered gingivorrhagia as a bleeding complication. Afterwards, INR were in TR. Asked about this fact, the patient told us he takes sildenafil every weekend but no longer stops ranitidine when he takes sildenafil.

Discussion. The standardization of OAT monitoring, patients' education and experience with coumarin dosage are the most outstanding factors to emphasize in our Anticoagulant Clinic. As a consequence, we detected two cases taking sildenafil and coumarin derivatives. Using the Naranjo ADR Probability Scale,[5] the relationship between sildenafil and INR increase in patients taking oral anticoagulants is highly probable. But, in the patient taking acenocoumarol once a day the INR modification is bigger than in the patient taking warfarin. In the first case, the INR modification coud be avoided by splitting the daily amount of acenocoumarol into two parts; in the second case, the patient suffered a bleeding complication as was observed in a published case associated with epistaxis,[6] but he decided not to stop ranitidine when he was taking warfarin. We think the different action of sildenafil on the two oral anticoagulants is a consequence of the different half-lives of these drugs, because sildenafil has high binding to plasma proteins

Table 1. INR measurements in patients teking oral anticoaugulants, before and after using sildenafil

	Before sildenafil INR	After sildenafil INR	
AC	3.05	7.7	
		3.1	Splitting AC daily dosage
		3.0	
		3.1	
		3.1	
W	2.5	4.4	
	2.5	4.2	
	3.2	5.9	gingivorrhage
		2.6	with ranitidin
		3.1	
		2.6	
		2.8	

AC=acenocoumarol; W=warfarin.

and is potentialy able to modify the plasma levels of oral anticoagulants. We think the interaction between these drugs is not produced on the cytochrome P450, because the effect of sildenafil at this level is weak, and the patients took the drug only once a week. In contrast, the most important interaction between sildenafil and coumarin derivatives takes place at the plasma level, through its plasma protein binding (93-96%) having more effect on coumarin derivatives with a shorter half-life. In any case, we must take into account that sildenafil increases the INR in patients taking acenocoumarol or warfarin, and they must be informed about a posible risk of bleeding complications.

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