Author's response to reviews

Title: Multiple Branch Retinal Vein Occlusions Associated with Quetiapine Fumarate

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Version: 2 Date: 20 May 2011

Author's response to reviews: see over
To,

The Editor in-charge,  
BMC Ophthalmology      20th May 2011

Dear Sir,

Point-by-point response for MS: 1442939295316667 - Multiple Branch Retinal Vein Occlusions Associated with Quetiapine Fumarate

Reviewer #1

1. This is a nice case report describing retinal vein occlusion after treatment with quetiapine fumarate. The report may be accepted after minor revision. Please indicate how you treated the patient and how was the final VA.

Response:
Changes made in the manuscript
Case Presentation, Paragraph 5, Line 5-8

“The patient was treated with oral lovastatin 20 mg daily. His lipid profile normalized after 2 months but the final visual acuity remained 0.33 and near visual acuity N24 at 33 cm due to the presence of hard exudates at the fovea.”

Added in the manuscript

2. In addition you may cite similar observations in other drugs such as


Response
We believe this is not necessary as the pathophysiologies of RVOs due to rofecoxib and quetiapine are not similar.
Reviewer #2

1. Please avoid using unnecessary abbreviations such as VA, RAPD, SGA.

Response:
Corrections performed as suggested by reviewer. All unnecessary abbreviations omitted.

Changes made in the manuscript

Case Presentation, Paragraph 2
He was a medium built individual with a body mass index of 24.83 kg/m^2 (height 165.5 cm, body weight 68 kg). Blood pressure was 122/74 mmHg with a regular pulse rate of 80 beats per minute. The visual acuity (VA) of his left eye was 0.33, with near visual acuity VA of N24 at 33 cm. The right eye had visual acuity VA of 1.0 and near vision of N6 at 33 cm. Confrontation test revealed a left central scotoma. Relative afferent pupillary defect (RAPD) was absent. Anterior segment examination for both eyes was normal. The intraocular pressure was 16 mmHg bilaterally.

Discussion, Paragraph 4
Quetiapine fumarate is a second generation antipsychotics (SGA) that is currently in use for the treatment of many psychiatric disorders. Unlike the older phenothiazine-type drugs, these atypical antipsychotics block both the dopamine-2 receptor and the serotonin 5-HT2A receptor; hence making them a versatile group of drug to treat a wide variety of psychiatric disorders. Another advantage of these second generation antipsychotics SGAs is the lower incidence of extrapyramidal side effects and tardive dyskinesia. The safety of these new atypical antipsychotics compared to the older phenothiazines is uncertain as they can cause serious metabolic side effects.

2. It is better to present the case as association of multiple BRVO and Quetiapine, as it may be just a coincidence.

Response:
As suggested by the reviewer, the title “Multiple Branch Retinal Vein Occlusions Associated with Quetiapine Fumarate” means that we are presenting the case as association of multiple BRVO and Quetiapine.
Reviewer #3

1. In the manuscript entitled “Multiple branch retinal vein occlusions associated with Quetiapine Fumarate” the authors report one case of a young man who developed branch retinal vein occlusions (BRVOs) while on Quetiapine Fumarate. The BRVO caused acute loss of vision in the left eye. The patient was on Quetiapine Fumarate for three years for a bipolar mood disorder. The patient appears to have developed an associated, but mild dyslipidaemia, from the Quetiapine Fumarate that was felt to contribute to the BRVO. Even though there is a link between dyslipidaemia and BRVO, the evidence in this case is not very strong since the patient’s dyslipidaemia is not severe and I suspect other factors may be playing a role in this case.

Response:

WE agree with the reviewer that the evidence in this case is not very strong. On one hand, WE can be complacent about it since the dyslipidaemia is not severe; hence cannot be a risk factor for BRVO in this patient. WE can wait until the dyslipidaemia become severe enough before WE act on it.

On the other hand, WE can be vigilant about the increasing levels of total cholesterol, triglyceride and LDL-cholesterol, and intervene before the patient develops a CRVO, stroke or any cardiovascular event.

WE also agree with the reviewer that other factors may be involved. In this case, his BMI also increased as a result of quetiapine treatment. His current weight is 68 kg compared to 62 kg prior to treatment.

Changes made in the manuscript
Case Presentation, Paragraph 2, Line 2:

“His body weight prior to quetiapine treatment was 62 kg.” added to the manuscript.
2. The authors conclude based on this case that, “atypical antipsychotic drugs have metabolic side effects which require regular monitoring........”. This conclusion is already well known among doctors who prescribe Quetiapine Fumarate since it has been associated with high triglycerides in 23 percent and high cholesterol in 16 percent of patients taking Quetiapine Fumarate.

Response:

WE agree with the reviewer that the above is a known fact. In this case report, WE try to highlight the importance of early intervention at the first sign of dyslipidaemia before the patient develops a CRVO, stroke or any cardiovascular event.
3. Since unintended reactions to medicines also referred to adverse drug reactions (ADRs) can occur, it is difficult to definitively and directly link Quetiapine Fumarate to this patient’s BRVO. .... This case is difficult to show the relationship since BRVOs are very common, the relationship may be coincidental and only marginally related.

**Response:**
WE agree with the reviewer that it is difficult to definitely and directly link Quetiapine fumarate to this patient’s BRVO. The purpose of a case report is **not to draw conclusion**, but to **generate a hypothesis** that there is an association between quatiapine fumarate usage and BRVO. This case report is intended to stimulate further research into the subject matter.

WE agree with the reviewer that BRVOs are indeed very common, but not in young adult. Lam et al found that only 1.7% of all branch retinal vein occlusions (BRVO) occurred in individual aged 49 or younger.

4. Symptoms that occur soon after a drug is taken are often easier to show cause and effect, especially when a rechallenge can be performed to confirm the link.

**Response:**
WE agree with the reviewer, this is especially true in cases of drug allergy.

Unfortunately, things are not always so straightforward. Rofecoxib was approved by FDA on May 20, 1999 for the treatment of osteoarthritis, acute pain conditions and dysmenorrhea. It was not until 2001 that rofecoxib was found to be associated with a significant increased risk of acute myocardial infarction compared with naproxen in the VIGOR study. But the authors of the study concluded that it was due to the cardioprotective effect of naproxen, rather than adverse effects of rofecoxib. In 2001, FDA requested Merck to introduce warnings on Vioxx labels that reflected the VIGOR study findings. Only in 2004 that Merck voluntarily withdrew Vioxx from the market. The increased risk of cardiovascular events persists even one year after stopping treatment.

(Baron JA et al. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. Lancet. 2008;372(9651):1756-64)
5. The supero-temporal retinal vein and the infero-temporal vein do not appear much different. The clinical photo is consistent with an acute brvo occurring at a second order venous branch that appears to originating one disc diameter along the major superior temporal vein. This should be reanalyzed and addressed.

Response:

WE agree with the reviewer that the supero-temporal vein and the infero-temporal vein do not appear much different at a glance. However if we reanalyzed and readdress the photo with higher magnification, the supero-temporal vein is more dilated than the infero-temporal vein.
6. Fluorescence angiogram would be very helpful in this case and should be added. The second smaller inferior temporal BRVO would need fluorescence angiogram evidence to confirm since I cannot be sure this is a definite BRVO based on the photo.

Response

WE agree with the reviewer that fluorescein angiogram (FA) is helpful. However WE did not perform FA at the time of diagnosis because WE felt that the risk of FA outweigh the benefit, since the confirmation of the second smaller inferior temporal BRVO will not alter our management. WE apologize to the reviewer.
7. On Figures 1 and 2 the hemorrhages appear mainly flame shaped it does not appear to follow any particular retinal vein.

Response
WE agree with the reviewer that flame-shaped hemorrhages do not follow any particular retinal vein. Flame-shaped hemorrhages are confined to the retinal nerve fiber layer and hence follow the retinal nerve fiber layer rather than retinal vein.

In BRVO due to atherosclerosis, the flame-shaped hemorrhages converged at the point of intersection of the retinal artery and vein.

In BRVO due to hyperviscosity syndrome (our patient), the point of occlusion can occur anywhere along the retinal vein. Hence the flame-shaped hemorrhages may appear randomly and do not necessarily begin at the retinal artery-vein intersection (white arrow).

Changes made in the manuscript
Case Presentation, Paragraph 3, Line 13-14:
“The retinal haemorrhages were oriented along the distal infero-temporal retinal nerve fiber layer but did not begin at the retinal artery-vein intersection.” Added to manuscript
8. Pigmentary spots involving the superior macular are unusual and need to be explained. They appear reminiscent of past focal laser treatment. **This should be addressed.**

**Response:**
The pigmentary spots are intraretinal lesions. Adjacent to these pigmentary spots are typical red blot hemorrhages (white arrows). WE believe that the" pigmentary spots" in the superior macular region are due to resolving blot hemorrhages.

The patient has never had any laser treatment before. There were no similar changes in the other eye.

![Image of eye with pigmentation and hemorrhages](image)

**Changes made in the manuscript**

Case presentation, Paragraph 3, line 4–6

“Intraretinal pigmentary spots with adjacent typical red blot hemorrhages believed to be resolving blot hemorrhages were seen. The patient has never had any laser treatment before”. Added to the manuscript
Color fundus photograph of the right eye (normal eye)
9. The retinal arterioles in all quadrants appear to be attenuated and there are increased arteriole reflexes with AV nicking. **The other eye should be checked for this finding too.**

**Response:**
The A:V ratio was 2:3 infero-temporally but was 1:3 supero-temporally. There were indeed increased arteriole reflexes with AV nicking which was confined only to the supero-temporal retinal artery of the left eye. The retinal arteries of the right eye were normal (picture above).

Rather than being a cause of the BRVO, WE believe this was a sequel of the BRVO in which hypoxia induced localized microglial cells proliferation along the right supero-temporal retinal artery; hence the increased arteriole reflexes with AV nicking only along the right supero-temporal retinal artery.


**Changes made in the manuscript**

**Case presentation, Paragraph 3, last 7–10**

“The arterio-venous ratio was 2:3 infero-temporally but was 1:3 supero-temporally. There were increased arteriole reflexes with arteriovenous nicking which was confined only to the supero-temporal retinal artery of the left eye.” added to the manuscript.

**Case presentation, Paragraph 3, last line**

Figure 3 included in the manuscript.

Previous figure 3, now changed to figure 4.

**Discussion, Last paragraph, Line 2–6:**

“The localized increased arteriole reflexes with arteriovenous nicking found only along the right supero-temporal retinal artery were believed to be the sequelae of BRVO rather than the cause of it. This is due to hypoxia which induced localized microglial cells proliferation along the right supero-temporal retinal artery.” Added to the manuscript.

**Reference 9(added)**

10. Other causes for this need to investigated since the patient’s mild and not very long standing dyslipidaemia seems out of proportion to this finding. Family history of vascular events, history of smoking, history of obesity, history of drug use or HTN would need to be investigated including a homocysteine level.

Response:
There was no family history of vascular events, no history of smoking or substance abuse, his BMI was 24.83 kg/m^2, and no history of hypertension.

WE did not check the homocysteine level. As far as homocysteine level is concern, there is debate whether homocysteinemia is a cause or a consequence of cardiovascular diseases. Furthermore, homocysteine-lowering therapy has not been proven to lower cardiovascular risk.


On the other hand, WE focused on dyslipidaemia because dyslipidaemia plays a central-role in cardiovascular disease whereby the chain of evidence is strongest for elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C).


**Changes made in the manuscript**

**Case presentation, Paragraph 1, last line**

“Sexual history was not significant and he has no history of substance abuse or smoking. There was no family history of vascular events as well.” Added to the manuscript
11. Additional follow-up and how the patient was treated would be helpful.

**Changes made in the manuscript**  
**Case Presentation, Paragraph 5, Line 5-8**

“The patient was treated with oral lovastatin 20 mg daily. His lipid profile normalized after 2 months but the final visual acuity remained 0.33 and near visual acuity N24 at 33 cm due to the presence of hard exudates at the fovea.”

Added in the manuscript

WE sincerely thank all 3 reviewers for their time and constructive input into our manuscript. WE hope BIOMED CENTRAL OPHTHALMOLOGY will accept our manuscript for publication.

As Edward de Bono once said:

“The need to be right all the time is the biggest bar to new ideas. It is better to have enough ideas for some of them to be wrong than to be always right by having no ideas at all.”

With kind regards,

Ku Chui Yong,
Tan Aik Kah,
Yeap Thye Ghee,
Lim Chee Siang
Mae-Lynn Catherine Bastion