Author's response to reviews

Title: Itraconazole associated Quadriparesis and Oedema

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Version: 2 Date: 28 October 2010

Author's response to reviews: see over
Dear Editor,

Thanks for giving us the opportunity to improve our case report before publication. We have considered the referees’ comments and have the following responses.

Referee 1:

i. **Table summarising neurophysiology findings**: We prefer to summarise the neurophysiology findings in the text. We feel inclusion of a detailed report including the numerical data would significantly lengthen the case report and is unlikely to be of further benefit to general readers.

ii. **Figure of nerve and muscle biopsy illustrating axonal loss and demyelination**: We have been enquired about obtaining images of the nerve and muscle biopsy but cannot obtain images from the overworked departments.

iii. **Was testing performed for antiganglioside and AntiGM1 antibody and campylobacter serology**: Unfortunately we did not perform these tests at the time.

Referee 3:

iv. **References for neuropathy due to voriconazole and posaconazole**. We have added following statement to the text ‘Among the other azole drugs, there are atleast four case reports of Voriconazole causing painful peripheral neuropathy in the literature [12,13,14] Whereas, Posaconazole despite being a highly lipophilic drug, has not been reported as an exclusive cause of neuropathy but illustrations that it enhances vincristine induced neurotoxicity are known [15,16]’.
v. Levels of itraconazole too high with standard dose – is there a reason and if neuropathy is related should levels be normally monitored: We have added following statement to the text. ‘It has been shown previously that Itraconazole levels are not only dose dependent but there have been significant variation in its concentrations in individuals receiving same dose probably reflecting its hepatic metabolism and enterohepatic circulation [22]. Hence, initial dosing cannot predict the steady state plasma concentration. Our case is an apt example for this as the initial level was high despite a standard dose. It is conceivable that higher levels lead to higher tissue saturation and are more likely to cause neuropathy and is advisable to monitor the levels at least during the initial dosing of the drug, and again after dose modification’.

vi. Change title from itraconazole induced.. to itraconazole associated...

: We accept this and have changed the title accordingly.

Referee 2:

vii. To add brief 2-3 lines about Vd of itraconazole and high lipophilic nature of this drug and hence prolonged elimination from adipose tissue - explains the prolonged neurological symptoms and complicating recovery:

We have added the following to the text. ‘Itraconazole has a high volume of distribution reflecting its high plasma proteins ability (99%) and high lipophilicity. The tissue concentration being 2-10 folds higher than plasma concentrations. The characteristic tissue penetrability has been deduced as the reason for its efficacy despite a very low plasma concentration in some individuals [20]. This tissue saturation and slow elimination may explain the prolonged nature of its neurotoxicity in our patient and the resulting slow recovery despite early drug discontinuation’.
viii. Regarding any other explanation for oedema i.e. TFT's and albumin:

We have added this statement to the text. “Thyroid function was normal during and after the acute illness and serum albumin was modestly reduced, ranging from 23 to 29 g/l during the illness. This could aggravate oedema but would not, of itself, be expected to give rise to the very marked oedema that was observed in this case.”

We hope the above responses are satisfactory to our referees and we thank them for their useful suggestions.

Many thanks.

Kind Regards

Yours sincerely,

Dr R Karadi
(On behalf of all authors)