Timing of sildenafil therapy in dialysis patients

Sir,

Dr Mohamed has described a case of hypotension in a 49-year-old haemodialysis (HD) patient during an inter-dialysis day on which he took a 50 mg dose of sildenafil citrate (Viagra®) and concludes that sildenafil was the most likely cause of this event [1]. As with many spontaneously reported adverse events, it is difficult to determine causality from the description given. In this case, the patient began to ‘feel unwell, with headache, nausea, epigastric pain and flushing’ 1 h after ingestion of sildenafil. When his blood pressure was measured the next day (12 h later), it was found to be 80/50. There is no way to be sure that the change in blood pressure occurred coincidentally with the onset of his symptoms.

Examination of the pharmacokinetic and haemodynamic profile of sildenafil in healthy volunteers and in haemodialysis patients does not support the association between sildenafil and hypotension in this case. In healthy volunteers, the maximum observed plasma concentrations (C_max) of sildenafil are reached within 30–120 min (T_max; median 60 min) of oral dosing in the fasted state and the terminal half-life (t_1/2) is 4–5 h. Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced mean maximum decreases in supine blood pressure of 8.4/5.5 mmHg. The reductions in blood pressure were most notable approximately 1–2 h after dosing and were not different from placebo at 8 h. This conclusion is supported by a recent Pfizer-sponsored study examining the pharmacokinetics of sildenafil in 16 HD patients. In this randomized crossover study, subjects received 50 mg doses of sildenafil 2 h before the start and 2 h after the completion of HD, 1 week apart [2]. The values for T_max, C_max, area under the concentration curve (AUC), and t_1/2 were similar to those observed in normal volunteers. Furthermore, the number of hypotensive events during HD was the same whether or not the subjects were or were not exposed to sildenafil during HD. Thus, it seems unlikely that the hypotension noted in this case more than 12 h after dosing was causally related to sildenafil.

Dr Mohamed has stated that sildenafil ‘has not been fully evaluated in this group of individuals’, which includes renal failure patients on dialysis. There have, in fact, been a number of studies reported to date showing that sildenafil is well tolerated in these patients. Paul et al. reported an open label study in nine patients on maintenance HD who were treated with sildenafil 50 mg of p.r.n. for 3 weeks. No side effects were reported by these patients [3]. Rosas et al. conducted a 4-week open-label study in which they treated 14 dialysis patients (average time on dialysis 3.8 yr). The maximum duration of sildenafil activity was noted as being 180 min. Two patients reported headache and one reported flushing. Sildenafil was well tolerated, and no major adverse effects were reported [4]. Chen et al. treated 21 peritoneal (PD) and HD patients in an open-label study for 6 months. The only side effects reported were headache (29%), visual disturbances (14%), dizziness (14%), nasal congestion (10%), and flushing (5%) [5]. Bellovich et al. studied 25 HD patients in a placebo-controlled 3-way crossover study (placebo, 25, and 50 mg sildenafil) consisting of 3 one-month treatment periods. Although significant efficacy was not observed, there were also no complications due to sildenafil in their group of patients [6]. DiPaolo et al. studied six HD and three PD patients in a 9-week, open-label, flexible-dose study. No adverse effects were reported, and they concluded that sildenafil may be safe and effective if correction of metabolic abnormalities does not improve ED [7]. MacDougall et al. reported only one headache and no other adverse events in a placebo-controlled crossover study in 16 PD patients [8]. Although combined, these studies include only 110 patients, the lack of significant side-effects reported, or effect of haemodialysis on the pharmacokinetics of sildenafil, suggests good tolerability among this patient group. In HD patients, during the post-HD period when they may be transiently volume depleted, it is reasonable to apply the same clinical considerations when using sildenafil as one would with any other vasodilating agent. It is not possible to completely rule out a causal effect of sildenafil in the hypotensive episode reported by Mohamed et al.; however, the known pharmacokinetic profile of sildenafil and the lack of such hypotensive effects in seven other studies summarized above make this highly speculative.

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Reply

Sir,
We were interested to read the comments by Drs Grossman and Siegel regarding our case report. There is no question that our patients suffered the recognized side-effects of sildenafil 1 h after taking the drug, namely headache, nausea, flushing and light headedness, at a time in keeping with the pharmacokinetic profile. From the published data it is unclear if the pharmacokinetic or pharmacodynamics in individuals who have recognized side-effects differ from those not effected and further work is needed in this area.

We failed to find another cause for his subsequent hypotension and would strongly support a temporal relationship with the sildenafil, despite the lack of correlation of pharmacokinetic data in the small studies quoted in renal failure patients. To further investigate the effect of sildenafil in the individual concerned a challenge dose would have to be given, though the patient himself is reluctant to consider this as it had no therapeutic benefit.

At the time of writing our case report, little evidence was available in the renal literature and, indeed, five of the references quoted by Grossman are either in abstract form at the ASN meeting in October 2000 or as yet unpublished.

In our unit, we have used sildenafil widely in our dialysis population, in many cases without notable side-effects. We would suggest, however, that some individual patients who are more sensitive to the drug, as characterized by the early onset of side-effects, may be also be at risk of developing subsequent hypotension during haemodialysis. We would maintain our prudence in advising the use of sildenafil in such individuals immediately post-dialysis or on non-dialysis days. Adverse side-effects may also raise the question as to whether there is interaction with other medication, or whether it is unmasking clinically silent cardiovascular disease.

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