We thank Professor Taylor for his interest in our paper[1] and for his helpful comments. We feel that we all agree that clozapine administration as crushed tablets suspended in an appropriate medium, or as a proprietary suspension or liquid formulation is a valuable dosing strategy in appropriate circumstances. In addition, it seems that giving clozapine in this way will on average give rise to significantly lower pre-dose plasma clozapine and norclozapine concentrations than if the same dose were prescribed as tablets.[1,2] Hence it is important to consider the mode of administration when reporting clozapine dose:plasma concentration relationships, for example.

As to the reason for this phenomenon, incomplete dosage due to sedimentation of either locally prepared, or proprietary suspension is but one possible explanation. Incomplete transfer to the patient of the desired volume of either suspension, or the liquid formation to which Professor Taylor refers is another, as is covert disposal of (part of) the administered dose after apparent ingestion. Clearly these factors will differ depending on individual circumstance and may indeed be influenced by the physical heath of the patient on the one hand, and by pressures on staffing on the other.

It is helpful to know that the liquid solution to which Professor Taylor refers is a clozapine solution in PEG (polyethylene glycol) 400. PEG 400 is clear, colourless, viscous liquid with a sweetish relatively unpleasant ‘plastic’ taste. This might help explain why 81 % of the patients studied by Oloyede et al. showed a preference for a proprietary suspension rather than the PEG 400 solution.[3] Moreover, because the viscosity of PEG 400 is some 120 times that of water at 20 °C, administration of the 50 mg/mL solution via a glass or other vessel gives the likelihood of solution remaining behind in the vessel. It is not clear how this situation is managed? Clearly rinsing the vessel with water will likely precipitate any remaining clozapine from the PEG solution.

As to the possible effects of mode of administration on clozapine pharmacokinetics, it seems unlikely to us that simply giving crushed tablets suspended in water or in orange juice, for example, by mouth would have any significant effect. What might be the mechanism of any such effect one wonders? As to administration of the liquid formulation, buccal absorption of clozapine might be considered a possibility. However, this would be expected to give improved bioavailability if anything because the first-pass effect would be by-passed. This is in part the reasoning behind the suggested use of intra-nasal clozapine.[4,5] Whether the presence of PEG 400 in the liquid formulation might affect matters is a further consideration, as of course is the wider topic of the widespread use of PEG-containing laxatives. We are not aware of any studies on these topics.

[458 words]

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