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LETTER TO THE EDITOR

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Impact of the CYP2D6 metaboliser status on the pupillary response of tramadol—a commentary

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Dear Editors,
This is to reply to the comments provided by Slanar et al to our article "The effects of tramadol on static and dynamic pupillometry in healthy subjects—the relationship between pharmacodynamics, pharmacokinetics and CYP2D6 metaboliser status" published in Eur J Clin Pharmacol (2005) 61: 257–266.

Slanar et al compared their own data [1, 2] with our work. However, there are some limitations to directly compare both studies:

- We used a placebo-controlled crossover study design. This allowed us to perform intra-subject comparisons between effects induced by either placebo and verum. This can be regarded as the highest possible level of standardisation within a clinical trial. The data obtained after administration of placebo can be used to evaluate possible background noise, diurnal rhythms or other influencing factors.
- We administered an immediate release formulation of tramadol, whereas Slanar et al used slow release capsules. As a consequence the studies can be expected to differ in the velocity of the PK/PD response.
- Furthermore, we performed a stereoselective bioanalytic method to differentiate between the enantiomers of tramadol and its +M1. This is crucial for pupillometry studies because the various enantiomers are known to contribute to a certain degree to either a μ or non-μ action component which are known to induce either decreases or increases of the pupil size.
- In addition to static pupillometry, we provided data from dynamic pupillometry. This added essential information, as tramadol administered to PMs was found to effect only dynamic pupillometry.

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In general, it appears to be difficult to directly compare drug-induced effects on pupil size between different studies. Important factors such as study design, accuracy of the measuring devices, sampling frequency, light conditions etc. may have a significant impact on the effects reported. We would therefore like to address those points in more detail.

In our study, we administered tramadol as an immediate release formulation, resulting in a faster absorption of tramadol, whereas Slanar et al used slow-release capsules. Accordingly, we observed maximum serum concentrations at 2 h for both tramadol enantiomers and between 2.5 and 3 h for both enantiomers of M1. Irrespective of the assumed subtype, the miosis in EMs gradually reached a maximum from 4 to 8 h after dosing in our study. This behaviour is well known for many drugs and can be attributed to an "effect compartment".

Slanar et al presented concentration-time profiles for heterozygous and homozygous EMs that were in good agreement with the known pharmacokinetic properties of tramadol. However, they provided no reasonable explanation for a discrepancy in the pharmacodynamic response pattern of those subjects. While in homozygous EMs a direct relationship between drug concentrations and miotic effects can be seen, heterozygous EMs behaved completely differently. Furthermore, although they describe a maximum effect in heterozygous EMs at 12 h, this was in fact the last observation. Thus it seems possible that maximum effect was not investigated by Slanar et al. We recommend that pharmacokinetic and pharmacodynamic parameters be measured until they return to baseline.

Although Slanar et al have used a slow release formulation, the pupillometric response for homozygous EMs appears to be comparable with our results. The miosis in EMs gradually reached a maximum from 4 to 8 h after dosing in both studies. It remains unclear why the slow release product did not delay the pharmacodynamic response. In comparison, the response-time profile obtained by Knaggs et al. [3] who used an intravenous route of administration showed a maximum miosis at approx. 150 minutes after dosing. It should be noted that we

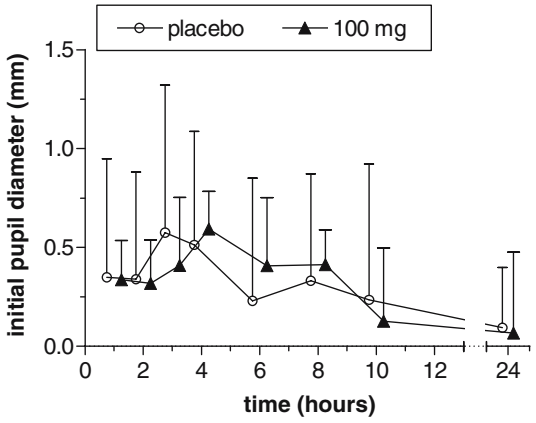

Fig. 1 Effects of placebo and tramadol-HCL in PMs. Data are represented as differences from baseline (i.e. predose)

performed pupillometry measurements much more frequently (8 times postdose) than did Slanar et al (4 time postdose). Less frequent PD measurements may miss important parts of the response-time curve such as start, maximum or end of effects.

In PMs, Slanar et al found a small miosis. A re-evaluation of our own data showed that this might be an non-specific effect. Fig. 1 shows that after treatment with both placebo and tramadol-HCl the pupil diameter increased. The effect was apparent immediately after dosing until 10 h thereafter. The reason for this remains unclear. Most probably sympathetic activation during day time might have been caused this small miosis. Furthermore, spontaneous oscillation of the pupil should be taken into consideration. We recommend caution in evaluating effects on the pupil diameter that range below 0.5 mm due to methodological limitations and, most important, the use of a placebo-controlled design.

Slanar et al differentiated the group of extensive metabolizers in homozygous and heterozygous extensive metabolizers. This was not the focus of our study, but we characterized the pharmacokinetics of tramadol stereoselectively in both metaboliser groups. Thus, both studies utilised different strategies and therefore deliver complementary results. In-depth comparison of both studies with respect to pharmacokinetics is not possible, as pharmacokinetic parameters (e.g. AUC, Cmax, Tmax, etc.) from Slanar et al are not available for assessment.

While it does make sense to compare point estimates (Cmax and Emax) and area measurements (AUC vs AUD) to each other, correlations of area measurements like AUC to point estimates seem questionable. The observed r_s are not very high (−0.39 and −0.41) and are in contrast to the positive r_s obtained from the respective comparisons for M1. The results cannot be regarded as conclusive in light of the many comparisons performed without using or at least mentioning some type of alpha adjustment. Interpretation of the metabolic ratios and the resulting effect correlations is problematic when tramadol and the M1 alone have effects in opposite directions.

In summary, Slanar et al add some interesting data on the static pupillometry in homozygous and heterozygous EMs treated with tramadol. These data were not in contrast to our work. However, two findings of Slanar et al need a careful re-evaluation. In contrast to the results obtained with homozygous EM, the miotic response of heterozygous EMs appears not to be correlated to the PK profile. Since the full time course of miotic effects has not been fully investigated and there was no placebo control, the significance of miosis in PMs is unclear.

Further studies are needed to clearly characterize the pupillary response pattern with respect to the CYP2D6 metaboliser status, including ultra-rapid, extensive, intermediate and poor metabolisers.

References

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