Model based meta-analysis (MBMA) to support the development of decision criteria in dental pain studies

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Objectives:

Pre-specified decision criteria for go/no go decision-making of a compound are critical in drug development, especially for novel mechanisms. Model based meta-analysis (MBMA) is a key component in this process estimating a distribution of effects over placebo for the endpoints of interest from observed trials. This enables determination of which endpoint is most sensitive and also helps quantify what a meaningful effect may be. MBMA was used to integrate prior information of drugs studied in the post-surgical dental pain model to quantify an effect over placebo for the endpoint (last observation carried forward) LOCF-based TOTPAR (area under the Pain Relief (PR) curve). PK/PD models were developed for a selective cyclooxygenase-2 (COX-2) inhibitor (SC-75416) on PR and clinical trial simulations were conducted to assist the study design[1]. This MBMA work provided the possibility to analyse the mean data from the literatures and to better handle trial to trial variability. It could be a generic approach prior to having PK/PD information for a particular compound.

Methods:

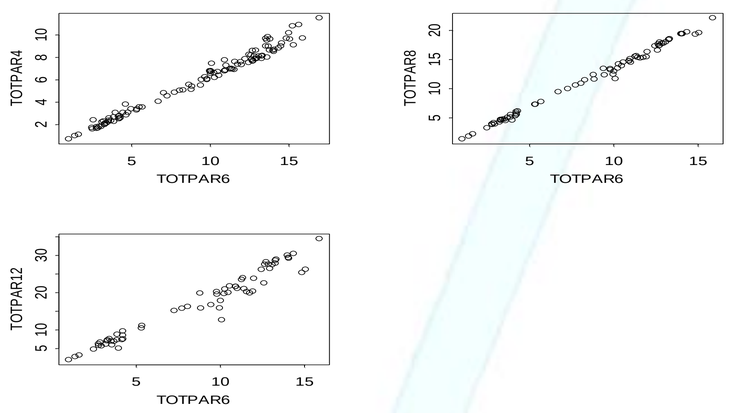
Database: Placebo controlled, post-surgical dental pain trials including NSAIDs, COX2 inhibitor or opiates reporting PR in subjects, following surgical extraction of at least 1 third molar post-operatively, were included in the meta-database. The analysis meta-data (TOTPAR6) consisted of 36 trials encompassing 101 treatment arms and 5882 subjects, in which of 23 trials for Ibuprofen, 8 trials for Rofecoxib, 7 trials for Valdecoxib, 1 trial for SC75416, Tapentodal or morphine. TOTPAR6 was derived from PR LOCF.

Meta-analysis: TOTPAR6 was chosen as the efficacy endpoint because it is well correlated with other TOTPARs (Figure 1) and commonly used as a primary endpoint. A nonlinear mixed effect method was utilised to analyse the of TOTPAR6 (0-6 hr post-treatment) from both internal and literature data. The drug effect was described by an E_{max} model and it was assumed that these drugs can achieve the same maximal effect with different potency (ED_{50k}). The model structure is expressed as below:

$$TOTPAR6_{ij} = E_0 + E_{max}*DOSE/(ED_{50k}+DOSE) + \eta_i + \varepsilon_{ij}$$

$TOTPAR6_{ij}$: observed response at jth arm of the ith trial
E_0: placebo effect
E_{max}: maximal drug effect, reflecting the maximal difference in response between placebo and active treatment
ED_{50k}: the dose for the kth drug reaching 50% Emax
η_i: random effect between trial variability assumed to be normally distributed with mean 0 and variance ω^2
ε_{ij} : residual variability assumed to be normally distributed with mean 0 and variance σ^2/N_{ij}
N_{ij}: sample size at jth arm of the ith trial

Figure 1. Correlation between TOTPAR4, 6, 8, and 12



Dose-response simulation: The fixed effect population parameter estimates and associated parameter uncertainty from the final model were used to predict the mean dose response for Ibuprofen at dose levels of 0, 100-800 mg. The simulations were repeated 1000 times.

Decision criteria: The information from meta-analysis aided determination of a minimum meaningful target value (TV) of TOTPAR6 change from placebo (ΔTOTPAR6) that would need to be observed in a dental pain study, with a certain level of probability, in order to further invest in the compound. Two decision rules governing the decision were evaluated for probability of being: i) superior to placebo; ii) greater than TV.

Results:

The dose-response data for TOTPAR6 was well described by the E_{max} model across the compounds (Figure 2). The parameters were well estimated (Table 1).

Reference:

[1] Kowalski KG et. al. Modeling and simulation to support dose selection and clinical development of SC-75416, a selective COX-2 inhibitor for the treatment of acute and chronic pain. Clin Pharmcol Ther. 83, 857-866 (2008)

Table 1. The main parameter estimates

Parameter	Estimates (RSE %)
E0	3.75 (6.8)
Emax	11.3 (5.22)
Log(ED50), ibuprofen	5.09 (3.87)
IIV(between trial variability)	1.31 (33.66)
Residual	8.68 (15.27)

Figure 2 The mean prediction for TOTPAR6 and observations across the compounds

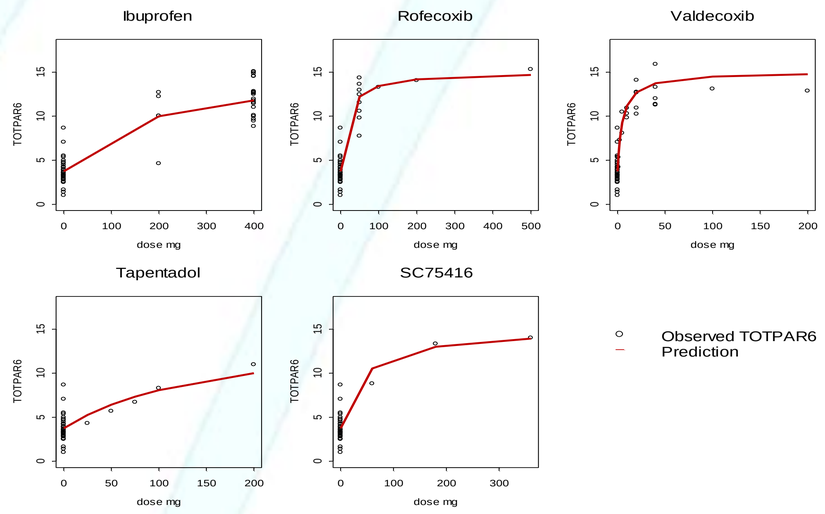
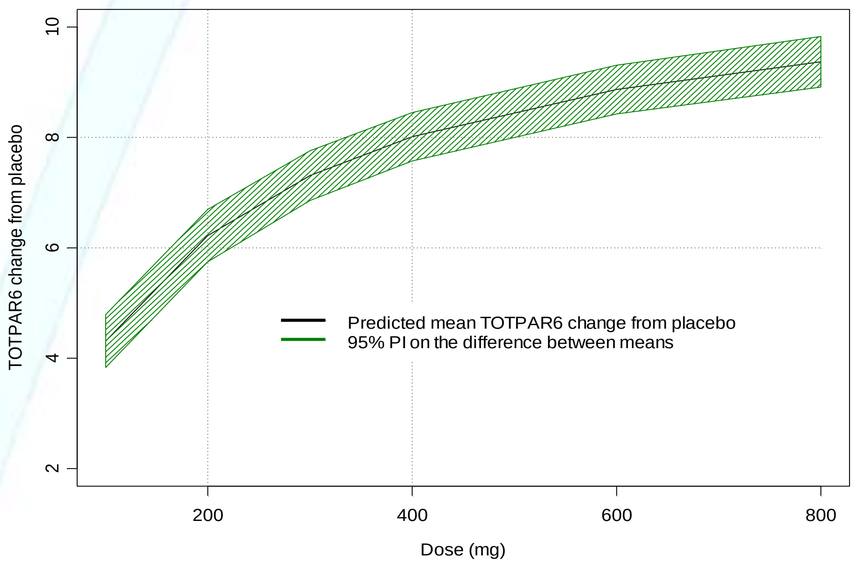
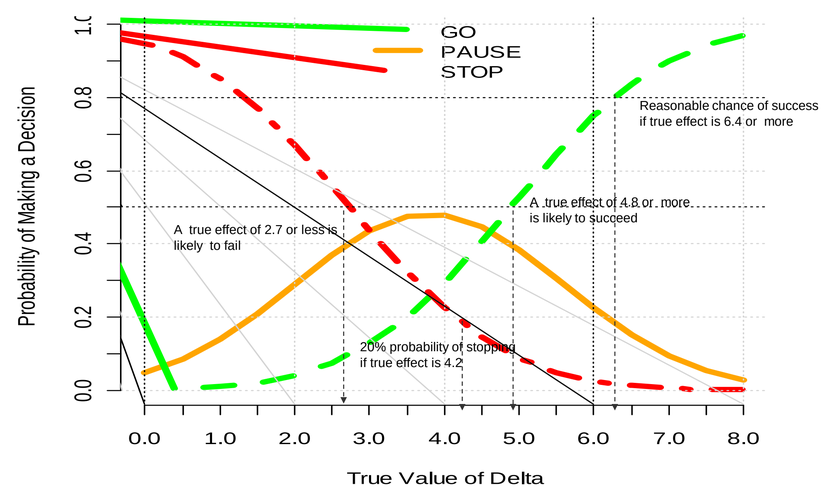


Figure 3. Predicted dose-response for Ibuprofen over placebo with parameter uncertainty (without IIV and residual)



Predicted mean [95%PI] TOTPAR6 change from placebo for 200mg and 400mg Ibuprofen were 6.22 [5.75,6.70] and 8.01 [7.57,8.45], respectively (Figure 3). Using this dose response information, and considering the main objective of the study, it was determined that a TV of 6 would be used as part of the decision criteria to progress a compound to the next stage. The (posterior) probability of the true effect being 6 would need to be at least 25 %, as well as at least 95% (posterior) probability of the true effect being greater than placebo. Figure 4 presents the decision criteria for making go/no go decision. Ibuprofen as a positive control will be included in the study and its response could help to interpret the study outcomes and guide the decision making. The potential impact of low or high Ibuprofen response on the probability of pause decision (Figure 4, orange area) will be explored at the next step.

Figure 4. Operational characteristics for TOTPAR6 over placebo



Conclusions:

This meta-analysis provided a broad overview and understanding of effect size of different classes of analgesic drugs in order to develop quantitatively target values for endpoints in early phase efficacy studies that do not have pre-defined meaningful values.

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