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MEETING ABSTRACTS

REACTIVATING EFFICACY OF OXIMES K203 AND K027 AGAINST A DIRECT ACETYLCHOLINESTERASE INHIBITOR IN RAT DIAPHRAGM: DOSE-RESPONSE MODELING

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In efficacy testing of experimental oximes, traditionally reactivation of OP-inhibited acethylcholinesterase (AChE) has been analysed by comparing the obtained effects of the single dose with the control [1]. However, quantitative analysis of *in vivo* dose-response data by benchmark dose (BMD) approach would improve both identification and quantification of the effect and it will allow more rigorous comparison of different oximes efficacies [2]. Thus, we have evaluated *in vivo* dose-response relationship for two promising experimental oximes, K203 and K027, concerning reactivation of diaphragmal AChE inhibited by dichlorvos (DDVP). To compare the oximes effects, BMD-covariate method was used to estimate oxime dose (with 90% confidence intervals) that elicits a pre-specified effect size of 50% (1.5-fold increase in AChE activity compared to DDVP-treated group). Wistar rats (5/group) were treated with oxime (0/1.25/2.5/5/25/50% LD_{50} *im*) immediately after DDVP challenge (75% LD_{50} *sc*). Activity of AChE was measured in rat diaphragm homogenates by modified Ellman´s method 60 min after the treatment. Dose-response modeling was done by PROAST software (version 65.5, RIVM, Nederlands). Exponential model m5-ab ($y=a[c-(c-1)\exp(-bx^d)]$) was selected as best estimate with parameters: a_{K203}=0.1525, a_{K027}=0.1498, b_{K203}=0.008472, b_{K027}=0.03941, c=2.117 and d=0.8916. Derived BMD_{50} were K203=117 (56, 209) and K027=21 (10, 37) µmol/kg bw, indicating that oxime K027 induces the same effect size with 5.5-times lower dose compared to oxime K203. Moreover, obtained confidence intervals of BMDs did not overlap allowing the conclusion that more potent dose-response relationship belongs to experimental oxime K027.

Keywords: dichlorvos; benchmark dose; oxime potency; rat diaphragm

References

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