

Phase 1c Trial Comparing the Anaesthetic Properties of Phaxan™ and Propofol

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Introduction: Phaxan™ (PHAX) is an aqueous solution of alphaxalone 10mg/ml and 13% 7-sulfobutylether beta-cyclodextrin. In preclinical studies PHAX is as fast onset and offset intravenous anaesthetic as propofol but with a wider therapeutic margin. The aims of this first in human study were to find the dose of PHAX that caused anaesthesia and to compare it with propofol for speed of onset and recovery, cardiovascular and respiratory effects and side effects.

Methods: This GCP-compliant study was registered with the Therapeutic Goods Administration under the CTN scheme and also listed on a clinical trials registry (ACTRN12611000343909). The trial was randomised, double blind, comparing the effects of propofol and PHAX using a Bayesian algorithm to determine dose equivalence for effects on the bispectral index (BIS). Male volunteers ASA grade 1 gave written informed consent (n=12 per group; propofol or PHAX). Assessments for 90 minutes after drug injection (single bolus dose) were: injection pain, involuntary movement, blood pressure, BIS, oxygen saturation, airway obstruction, the Richmond Agitation and Sedation Scale (RASS) and the Digit Symbol Substitution Test (DSST).

Results: PHAX was clear and water-like. No subject complained of pain on injection with PHAX whereas 8 of the 12 subjects given propofol did. Involuntary muscle movement was observed in the propofol-treated group (3 of 12) and in 0 of 12 PHAX-treated subjects. 11 subjects given propofol 3.0 (3.00-1.87; median, 75/24IQ) mg/kg and 11 subjects given PHAX 0.5 (0.55-7; median, 75/24IQ) mg/kg reached a BIS value of 50 or less; lowest average BIS reached being 30 and 31 respectively for propofol and PHAX treated subjects with no significant differences between treatments for timing of onset and recovery of BIS. PHAX caused less depression of systolic and diastolic blood pressure (p<0.0001 Wilcoxon matched Pairs); 9% v 18%, for systolic and 16% v 29% for diastolic in PHAX and propofol treated subjects respectively. Further, 8 of the 12 propofol-treated subjects and 1 of 12 PHAX-treated subjects had an obstructed airway (p = 0.0094; Fisher's exact test). For subjects reaching a BIS of 50 or less the assessments of recovery were:

BIS returned to 90 at 21(3.6) and 21 (3.5) [mean(sem)] minutes after propofol and PHAX respectively;

a RASS score of 0 was reached 5(10-20) and 17.5(10-20) [median(75%IQ); p=0.0925] minutes after propofol and PHAX respectively;

DSST scores returned to pre drug injection values 53.1(8.4) and 54.4(7.0) [mean(sem)] minutes after propofol and PHAX respectively;

There was no increase in C3 and C4 complement fraction levels 5 and 15 minutes after injection of either drug. No subject reported an adverse or unpleasant experience.

Conclusions: Alphaxalone 10mg/ml in an aqueous solution with 13% 7-sulfobutyl ether beta cyclodextrin (PHAX) causes fast onset short duration anaesthesia equivalent to propofol but with less cardiovascular and respiratory depression and no pain on injection. The induction dose and duration of anaesthesia with PHAX is the same as that reported previously for alphaxalone formulated as Althesin¹. PHAX may be an alternative to propofol for intravenous anaesthesia.

References: 1) Clarke RS, Dundee JW, and Carson IW. A new steroid anaesthetic-Althesin. Proc R Soc Med. 1973; 66(10): 1027–1030.