Phase1c trial comparing the anesthetic properties of Phaxan™ and propofol

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Introduction:

Alphaxalone is a neuroactive steroid anesthetic. This water-insoluble drug, formulated as Althesin using CremophorEL to dissolve it, was an intravenous anesthetic used widely in clinical practice from 1972-1984[1]. Althesin was withdrawn from the market because of hypersensitivity to the CremophorEL. Phaxan™ (phax) is an aqueous solution of alphaxalone 10mg/ml and 13% 7-sulfobutylether beta-cyclodextrin [betadex; Dexolve, a molecule with a lipophilic cavity that enables drug dispersal in water for human use]. In preclinical studies phax is as fast onset and offset intravenous anesthetic as propofol with less effect on blood pressure and a therapeutic index (TI) greater than 30 (TI of propofol is 6). The aims of this first in human study, GCP compliant study, were to find the dose of phax that caused anesthesia and to compare it with propofol for speed of onset and recovery, cardiovascular and respiratory effects and side effects such as involuntary movements and pain on injection.

Methods:

The study was approved by Monash Health Ethics Committee, registered with the Therapeutic Goods Administration under the CTN scheme and also listed on a clinical trials registry (ACTRN12611000343909). The trial design 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). 24 male volunteers ASA grade 1 gave written informed consent (n=12 per group; propofol, phax).

Parameters assessed after drug injection (single bolus dose) were: injection pain, involuntary movement, blood pressure, bispectral index (BIS), oxygen saturation, incidence of apnoea or airway obstruction >30 seconds and the need for airway support. Recovery from sedation was assessed with the Richmond Agitation and Sedation Scale (RASS) and the Digit Symbol Substitution Test (DSST). Arterial blood was withdrawn for complement levels.

Results:

Eleven subjects given propofol 2.43 (3.00-1.87; median, 75/25 IQ) mg/kg and 11 subjects given phax 0.5 (0.55-0.47; median, 75/25 IQ) mg/kg reached a BIS value of 50 or less; lowest average BIS reached being 30-31 for both propofol and phax-treated subjects with no significant differences between treatments for timing of onset and recovery of BIS (**figure 1**). A cohort of those subjects received doses between the 75/25 IQ range of each agent (n = 8 propofol and n = 9 phax-treated subjects). They caused the same profile for BIS depression and recovery (**figures 1B, 1D**) and so they were used to compare the two agents for other effects. In those subjects, there were statistically significant differences between propofol and phax-treated subjects in cardiovascular effects (**figure 2**). The average maximum drop in blood pressure was 13% v 20%, for systolic and 19% v 38% for diastolic in phax and propofol treated subjects respectively. Further, 9 of the 12 propofol-treated subjects and 0 of 12 phax-treated subjects had apnoea or obstructed airway > 30 seconds (**table 1C**). The results of other assessments were:

- BIS returned to 90 at 21(2.2) and 21 (3.0) [mean(sem)] minutes after propofol and phax respectively;
- RASS score, depressed to -4 by both drugs, recovered to 0 at15(10-20) and 5(5-10) [median(75/25 IQ)] minutes after propofol and phax respectively (**table 1B**);
- DSST scores returned to pre drug injection values 35 minutes after propofol and phax respectively (**table 1A**).

Pain on injection only occurred in propofol-treated subjects (8 out of 12; **table 1C**). Involuntary muscle movement and emergence delirium were observed solely in the propofol-treated group (3 of 12; **table 1C**). There was no increase in C3 and C4 complement fraction levels 5 and 15 minutes after injection of either drug.

Conclusions:

Alphaxalone 10mg/ml in an aqueous solution with 13% 7-sulfobutyl ether beta cyclodextrin (phax) causes fast onset short duration anesthesia equivalent to propofol but with less cardiovascular and respiratory depression and no pain on injection. The induction dose and duration of anesthesia with phax is the same as that reported previously for alphaxalone formulated as Althesin[2]. Therefore phax can be expected to be an alternative to propofol for anesthesia, sedation and ICU practice.

Reference:

1. Prys-Roberts C, Sear J. Steroid Anaesthesia. Br J Anaesth 1980; 52(4):363-5
2. Clarke RS, Dundee JW, and Carson IW. A new steroid anaesthetic-Althesin. Proc R Soc Med. 1973; 66(10): 1027–1030.

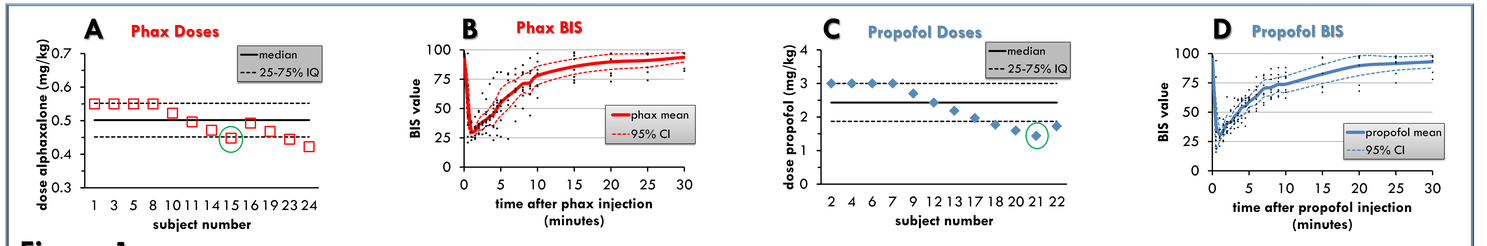

Figure 1: The dose of drug given to each subject (Y axis) v the subject trial number, for phax subjects (**A**) and propofol-treated subjects (**C**). All subjects reached a BIS<50 except subject 15 (phax) and subject 21 (propofol) shown by a green circle around the datum point. These graphs show the effect of the Bayesian design - a progressive 10% dose reduction until one subject did not reach a BIS<50 (subjects 15 and 21). Subjects 16 and 22 had 20% increase in dose and all subjects after them received 10% smaller drug dose because the previous subject attained a BIS < 50. The time to achieve BIS < 50 [mean (95% CI)] was 36 (22-45) seconds for propofol and 36 (28-44) in phax-treated subjects; n = 11 each. The time to onset of peak sedative effect was the same for both drugs i.e., less than 1.5 minutes. The doses of drug that caused BIS<50 were combined for each group (N = 11 each for phax and propofol) to calculate median and interquartile range shown by horizontal solid and dashed lines on graphs A and C. The cohort of subjects that received doses within that interquartile range (9 phax and 8 propofol subjects) were used for comparison of the two drugs' effects on the time response relationships of BIS (**B** and **D**) and also cardiovascular parameters (**Figure 2**), and rate of recovery (DSST and RASS) – see **table 1**.

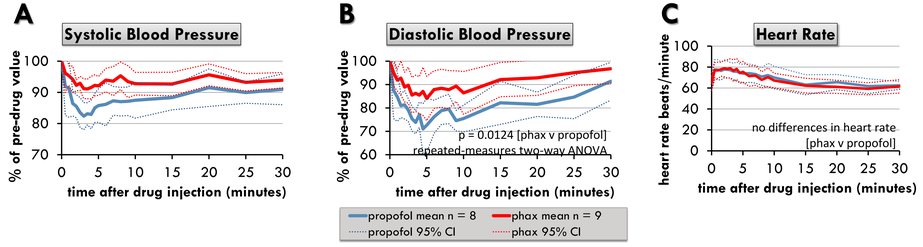

Figure 2: The graphs show the blood pressure and heart rate measurements for the nine subjects that received phax 0.52 (0.49-0.55) [median (25/75 IQ)mg/kg] and the eight subjects that received propofol 2.85 (2.37-3) [median (25/75 IQ)mg/kg]; doses shown to cause equal effect in speed of onset and offset, duration and depth of depression of BIS shown in **Figure 1**. Propofol caused significantly greater falls in systolic (**A**) and diastolic (**B**) blood pressure with no difference in heart rate effect between the two anesthetics. (**C**)

A

DSST scores		before	35 min post anesthesia
propofol n = 8	mean	73	69
	sem	5	5
	n	8	8
phax n = 9	mean	72	69
	sem	3	3
	n	9	9

B

RASS score		time after anesthetic injection (minutes)					
		*5	10	15	20	25	30
propofol n = 8	median	*-3	0	0	0	0	0
	IQ	-5	-2	-1	0	0	0
		1	0	0	0	0	0
phax n = 9	median	*0	0	0	0	0	0
	IQ	-3	0	0	0	0	0
		0	0	0	0	0	0

C

Incidence of Side Effects	propofol n = 12	phax n = 12	Fisher's exact test p value
apnoea or airway support	9	0	0.003
pain/discomfort on injection	8	0	0.0013
involuntary movement	3	0	
emergence delirium RASS > 0	3	0	
nauseated	0	0	

Table 1: Table **A** shows the scores obtained from the Digit Symbol Substitution tests applied 5 minutes before and 35 minutes after anaesthesia in phax-treated subjects [0.52 (0.49-0.55); median (25/75 IQ)mg/kg] and propofol-treated subjects [2.85 (2.37-3); median (25/75 IQ)mg/kg]. Table **B** shows the RASS scores measured every 5 minutes after anesthetic injection.. * denotes p < 0.05 Fisher's exact test; faster early recovery to RASS = 0 after phax. Table **C** shows the side effects following propofol and phax. Propofol caused significantly more respiratory depression and pain on injection.. Involuntary movements and emergence delirium only occurred in propofol-treated subjects.