**PhaxanCD™**, a Captisol®-enabled water soluble preparation of alphaxalone for intravenous anesthesia and sedation: comparison of anesthetic properties with propofol and Althesin®

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**Introduction**

Alphaxalone is a neuroactive steroid that causes anesthesia by positive modulation at GABA receptor. It was the main ingredient of Althesin®, used widely for intravenous anesthesia from 1971 until 1984 when it was withdrawn from clinical practice because of hypersensitivity to Cremophor EL the emulsifying agent used in the formulation (1). Many attempts have been made to reformulate this compound for human use because of its favourable anaesthetic and safety profile but hitherto those attempts have failed to prepare a suitable water based preparation. Captisol™ is 1,3-sulfobutyl ether beta-cyclodextrin; a molecule with a lipophilic cavity, that enables water insoluble drug dispersion in water for human use.

**Objectives**

1. assess anesthesia and recovery using this preparation and
2. compare these properties with propofol and Althesin®

**Materials and Methods**

A solution of alphaxalone [10mg.ml⁻¹](PhaxanCD™) was prepared by dissolving alphaxalone 300mg (0.9 millmoles) in saline 8.9% 30ml, using Captisol® (7-sulfobutyl ether beta cyclodextrin) 3889mg (1.8 millmoles); this produced a solution with a complexation ratio alphaxalone:Captisol® of 1:2. An “Althesin®-like” solution of alphaxalone in 20% Cremophor EL (ALTH) was prepared as described in the literature (2). Male Wistar rats (wt 150-220g) were implanted with indwelling internal jugular vein intravenous catheters under halothane anesthesia. Twenty four hours later each rat received an intravenous injection from a range of doses of either PHAX or ALTH (1.25, 2.5, 5, 10, & 15 mg.kg⁻¹), or propofol emulsion [10mg.ml⁻¹ propofol; PROPF] (1.25, 2.5, 5, 10, 15, & 20mg.kg⁻¹); n = 10 rats per dose. Three more groups of 10 rats each were given vehicle only instead of the anesthetic solutions [13% Captisol®, 20% CremophorEL, 10% lipid emulsion]. The following were assessed at regular time intervals after the intravenous injection:

- righting reflex: 1 normal; 2 slow; 3 some attempt; 4 none
- tail pinch response: 1 normal; 2 weak; 3 just present; 4 none
- time the rat was able to walk on the rotarod (a rotating cylinder) measured in seconds: the maximal normal run time is 120 s in non sedated rats – this was a measure of time taken to attain full recovery from the sedating effects of the anesthetic injections.

Results from groups of ten rats treated with the same anaesthetic and dose were combined for statistical purposes. Rats that attained a score of 4 for loss of righting reflex were deemed to have lost consciousness and those that scored a 4 for loss of tail pinch response were deemed to be surgically anaesthesised. The number of rats in each group of 10 similarly treated animals that scored 4 were subjected to probit regression analysis using

**Results**

Alphaxalone (10mg.ml⁻¹) dissolved readily in 13% Captisol®-saline solution. The resultant solution was colourless and completely clear. It did not cause stiction when used in plastic syringes.

Intravenous PHAX caused immediate dose-related sedation and anesthesia accompanied by no abnormal movements. The graphs show the probit plots for anaesthetic end points for righting reflex and tail pinch responses. Also shown are graphs of the mean walking time on the rotarod for groups of 10 rats at each dose of the three anesthetic preparations.

The table below summarises the results taken from these graphical plots. It can be seen that PhaxanCD is equipotent with Althesin® in causing unconsciousness and surgical anaesthesia and both are more potent than propofol in this respect. Recovery from unconsciousness caused by PhaxanCD is just as fast as with propofol. Control experiments revealed that the vehicles given alone intravenously, 20% CremophorEL, 10% lipid emulsion and 13% Captisol had no sedating or anesthetic effects.

**Conclusions**

PhaxanCD™ causes anesthesia with fast onset, and offset timing equal with propofol and Althesin®, the former commercial human anesthetic formulation of alphaxalone.

PhaxanCD™ is twice as potent as propofol.

PhaxanCD™ is a clear water-soluble preparation using an FDA-approved excipient to achieve water solubility—Captisol®. This avoids the only impediment to alphaxalone being used clinically for human anesthesia in todays operating rooms, i.e., hypersensitivity reactions to CremophorEL. This advance will allow the reintroduction of this useful agent into human anesthesia practice.

**Reference List**