The Role of Phaxan™ in Neurology and Neurosurgery?

a discussion of preclinical and clinical data

INTRODUCTION

Recent pre-clinical and clinical studies have shown that the properties of the new aqueous preparation of the anaesthetic steroid alphaxalone (Phaxan™) are exactly the same as those described previously for the CremophorEL formulation of alphaxalone, (Althesin®) that was used extensively in clinical anaesthetic practice from 1972-1984; the same speed of onset and duration of anaesthesia and sedation, very high safety profile but without the CremophorEL-induced hypersensitivity [1,2]. These results strongly suggest that Phaxan™ will have the same clinical profile and utility as Althesin® *sans* hypersensitivity reactions

This article describes the utility of Phaxan™ in the treatment of status epilepticus, head injury and stroke, and neurosurgical anaesthesia.

When Althesin was being marketed and used clinically, one sub specialty of anaesthetic practice was markedly changed by the introduction of the agent; neuroanaesthesia. The big advantages of Althesin® in this field of practice were the cardiovascular stability and fast predictable awakening, a powerful anticonvulsant effect combined with the drug's ability to control cerebral metabolic rate and intracranial pressure.

What follows below is a review of published data that point to the properties, effects and uses that can be expected from using Phaxan™ in the place of Althesin® for anaesthesia and sedation in neurosurgery and neuro-intensive care.

pre clinical data

antiepileptic activity

Several animal models have been used to demonstrate the anticonvulsant properties of alphaxalone. Alphaxalone produced potent anticonvulsant effects and completely suppressed the development of kindling in pentylenetetrazole-kindled mice [3]. Two other forms of experimental epilepsy in rabbits [generalized (oxygen at high pressure-induced seizure) and partial (penicillin cortical-induced seizure)] also revealed that

[1] Goodchild et al 2015. Alphaxalone Reformulated: A Water-Soluble Intravenous Anesthetic Preparation in Sulfobutyl-Ether-β-Cyclodextrin. Anesthesia and Analgesia:120(5); 1025-1031

[2] Monagle et al 2015: A Phase1c Trial Comparing Efficacy and Safety of a New Aqueous Formulation of Alphaxalone with Propofol. Anesthesia and Analgesia:*in press*

[3] Hansen SL, Sperling BB, Sanchez C. Anticonvulsant and antiepileptogenic effects of $GABA_A$ receptor ligands in pentylenetetrazole-kindled mice. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:105-13.

Althesin® possessed anticonvulsant properties [4]. Potentiation of the anticonvulsant effect of benzodiazepines by sub anaesthetic dose of alphaxalone has also been demonstrated [5]. By contrast Peterson [6] evaluated the anticonvulsant activity of Saffan® (veterinary preparation of Althesin®) administered **alone** in two rat models of epilepsy: maximal electroshock and subcutaneous pentylenetetrazole seizures. Sedation was tested in each animal just prior to the seizure test to differentiate selective antiepileptic effects from nonselective anticonvulsant or anaesthetic activity. In both seizure models Saffan® induced anticonvulsant activity but only at doses associated with sedation.

Using Sprague-Dawley rats, Wardley-Smith et al [7], determined the anticonvulsant potencies of Althesin®, ketamine and methohexitone for bicuculline and strychnine-induced seizures. All three anaesthetics protected against both types of chemically-induced convulsions; the degree of protection varied from 34 to 151%, with Althesin® being the most effective. These data suggested that the order of anticonvulsant potencies at equivalent anaesthetic concentration was Althesin® >> ketamine = methohexitone [7].

cerebral metabolism and intracranial pressure

When a clinician treats a patient who is undergoing neurosurgery or possibly receiving intensive care for the management of cerebral trauma or stroke, any therapeutic regimen necessarily involves attempts to control intracranial pressure and cerebral metabolic rate. Anaesthetic drugs are used to inhibit neuronal activity in the brain, thus leading to a decrease in the demand for supply of oxygen and nutrients that may be limited by brain swelling. In 1972 Pickerodt et al reported that Althesin® anaesthesia caused a fall in intracranial pressure without significant falls in blood pressure [8,9]. This is achieved clinically by dose titration to achieve depression of brain electrical activity (EEG) to "burst suppression".

Vijn and Sneyd (1998) [10] studied several intravenous anaesthetics in rats using burst suppression ratio (BSR) detection in the extradural EEG. After bolus injection, peak BSR values of 95% were achieved with propofol 8 mg kg-1, etomidate 3.5 mg kg-1 and alphaxalone 4.5 mg kg-1. Thiopental 32 mg kg-1 produced a peak BSR of 70% (larger doses were not tolerated). Recovery was fastest with propofol, followed by etomidate and alphaxalone with equal duration, and slowest with thiopental. The usefulness of thiopental and propofol was limited by their depression of blood pressure and cerebral perfusion. It was subsequently shown that etomidate infusions caused deaths in intensive care by adrenocortical depression [11]. Only the alphaxalone formulation had the desired neurological effects and safety characteristics.

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[4] De Riu PL, Susini G, Ruju P. Anticonvulsant activity of Althesin on experimental epilepsy. Br J Anaesth 1982;54:343-7.

[5] Deutsch SI, Rosse RB, Steinberg K, et al. Evaluation of in vivo interactions in mice between flurazepam and two neuroactive steroids. Pharmacol Biochem Behav 1996;55:323-6.

[6] Peterson SL. Anticonvulsant profile of an anesthetic steroid. Neuropharmacology 1989;28:877-9.

[7] Wardley-Smith B, Little HJ, Halsey MJ. Lack of correlation between the anaesthetic and anti-convulsant potencies of althesin, ketamine and methohexitone. Br J Anaesth 1988;60:140-5.

[8] Pickerodt V, McDowall DG, Coroneos NJ, Keaney NP. Effect of Althesin on carotid blood flow and intracranial pressure in the anaesthetized baboon: a preliminary communication. Postgrad Med J 1972;48:Suppl-61.

[9]Pickerodt VW, McDowall DG, Coroneos NJ, Keaney NP. Effect of Althesin on cerebral perfusion, cerebral metabolism and intracranial pressure in the anaesthetized baboon. Br J Anaesth 1972;44:751-7.

[10] Vijn PC, Sneyd JR. I.v. anaesthesia and EEG burst suppression in rats: bolus injections and closed-loop infusions. Br J Anaesth 1998;81:415-21.

[11] Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. Anaesthesia 1984;39(10):973-81.

clinical data

antiepileptic activity

The anticonvulsant effects of Althesin® have been shown in humans mirroring the preclinical results above. Its use in electroconvulsive treatment (ECT) was common because of its fast recovery rate [12]. Gran et al [13] assessed seizure duration in unilateral ECT recorded by means of EEG in an intra individual comparison of etomidate 0.3 mg/kg and Althesin® 0.6 mg/kg with methohexitone 1 mg/kg body weight. The patients were intubated and alveolar CO_2- and O_2-concentrations kept constant at 3% (3 kPa) and 92% (92 kPa) respectively. Seizure duration was the same when either etomidate or methohexitone were used, whereas Althesin® significantly shortened seizure duration in comparison with methohexitone. Local pain on injection and subsequent superficial thrombophlebitis occurred frequently with methohexitone. This did not occur with etomidate or Althesin® [14].

status epilepticus

Althesin® has been described in the successful treatment of severe cases of drug resistant status epilepticus [15]. In that paper Munari et al reported the successful treatment of eight out of eleven patients with status epilepticus that had failed to respond to standard treatments. All eleven patients had continued to have seizures even though very large doses of conventional antiepileptic drugs had been administered. Eight of those cases stopped fitting once treated with Althesin®. In that paper is shown an EEG recording (labeled figure 1) in which 4 ml Althesin® (36mg alphaxalone) abolished totally all aberrant brain electrical activity. That subject then became free of epileptic fits for twelve days [15].

cerebral metabolism and intracranial pressure

Althesin® has been shown in a number of studies in humans to decrease cerebral metabolism and thus cerebral blood flow and intracranial pressure, without significant cardiovascular depression - properties useful in neuroanaesthesia and in the management of brain injury [16,17,18].

The effects of 142 intravenous boluses of Althesin® (0.05 ml/kg which is an anaesthetic induction dose) on cerebral perfusion pressure (CPP) were studied by Procaccio et al (1988; [19]) in twelve head injured comatose

[12] O'Carroll TM, Blogg CE, Hoinville EA, Savege TM. Etomidate in electroconvulsive therapy. A within-patient comparison with alphaxalone/alphadalone. Anaesthesia 1977;32:868-72.
[13] Gran L, Bergsholm P, Bleie H. Seizure duration in unilateral electroconvulsive therapy. A comparison of the anaesthetic agents etomidate and Althesin with methohexitone. Acta Psychiatr Scand 1984;69:472-83.
[14] Gran L, Bergsholm P, Bleie H. Seizure duration in unilateral electroconvulsive therapy. A comparison of the anaesthetic agents etomidate and Althesin with methohexitone. Acta Psychiatr Scand 1984;69:472-83.
[15] Munari C, Casaroli D, Matteuzzi G, Pacifico L. The use of althesin in drug-resistent status epilepticus. Epilepsia 1979;20:475-83
[16] Sari A, Maekawa T, Tohjo M, et al. Effects of Althesin on cerebral blood flow and oxygen consumption in man. Br J Anaesth 1976;48:545-50
[17] Takahashi T, Takasaki M, Namiki A, Doi S. Effects of althesin on cerebrospinal fluid pressure. Br J Anaesth 1973;45:179-84
[18] Turner JM, Coroneos NJ, Gibson RM, et al. The effect of althesin on intracranial pressure in man. Br J Anaesth 1973;45:168-72.

patients. The authors found that Althesin® was beneficial if its use was guided by the minimum voltage of the CFM trace. Similar results were found by Dearden and McDowall in 1985 [20]. By 1983, just before its withdrawal from the market, Althesin® was in mainstream intensive care treatment of head trauma and brain injury [21] and also in neurosurgery and neuroradiology [22,23].

neurosurgery

The useful properties of Althesin® have been shown to be beneficial during neurosurgical operations. Ten patients with small supratentorial tumours were anaesthetised and studied during craniotomy by Bendtsen et al [24]. Cerebral blood flow (CBF) was measured in the contralateral hemisphere by a modification of the Kety and Schmidt technique using xenon-133 intravenously. With an Althesin® infusion rate of 0.2 ml/kg/h, CBF was 24.4 ± 5.4 $ml.min^{-1}$/100 g and CMRO2 1.87 ± 0.44 $ml.min^{-1}$/100 g at $PaCO_2$ 4.1 ± 0.7 kPa (mean ± SD). During constant infusion rates of Althesin®, steady values of $CMRO_2$ were obtained, while an increase in infusion rate of 150% was associated with an increase in plasma alphaxalone concentration, a decrease in $CMRO_2$ and a tendency of further EEG suppression [24].

CONCLUSION

Phaxan™ can achieve the same therapeutic effects with the same dose of alphaxalone as did Althesin® and with the same safety and timing of onset and duration of effect. Therefore, once it is introduced into clinical practice Phaxan™ is expected to be particularly indicated for:

- anaesthesia for neurosurgery
- intensive care management of status epilepticus, head injury and stroke

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[19] Procaccio F, Bingham RM, Hinds CJ, Prior PF. Continuous EEG and ICP monitoring as a guide to the administration of althesin sedation in severe head injury. Intensive Care Med 1988;14:148-55.

[20] Dearden NM, McDowall DG. Comparison of etomidate and althesin in the reduction of increased intracranial pressure after head injury. Br J Anaesth 1985;57:361-8

[21] Moss E, Gibson JS, McDowall DG, Gibson RM. Intensive management of severe head injuries. A scheme of intensive management of severe head injuries. Anaesthesia 1983;38:214-25.

[22] Dallas SH. Total intravenous anaesthesia for neurosurgery and neuroradiology. Anaesthesia 1980;35:462-6.

[23] Rasmussen NJ, Rosendal T, Overgaard J. Althesin in neurosurgical patients: effects on cerebral hemodynamics and metabolism. Acta Anaesthesiol Scand 1978;22:257-69.

[24] Bendtsen A, Kruse A, Madsen JB, et al. Use of a continuous infusion of althesin in neuroanaesthesia. Changes in cerebral blood flow, cerebral metabolism, the EEG and plasma alphaxalone concentration. Br J Anaesth 1985;57:369-74.