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**TITLE :** ANTAGONISM OF VECURONIUM BY ONE OF ITS METABOLITES IN VITRO  
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Resistance to vecuronium (Vec) after its long term application has been reported in ICU patients [1]. As Vec is degraded to different active metabolites, we aimed to elucidate the possible role of these metabolites in the above observation and investigated the interaction of 3-decacyl Vec (3-OH Vec) and 3,17-bisdesacyl Vec (3,17-OH Vec) with its parent compound in vitro using the standard rat hemidiaphragm-phenic nerve preparation.

After approval by the local Committee on animal research the dose response relationship of Vec, 3-OH Vec and 3,17-OH Vec was established in the first part of the study (6 diaphragms each). In the second part the dose response relationships of 3-OH Vec and 3,17-OH Vec was studied in the presence of an ED<sub>25</sub> of Vec in additional 12 diaphragms. Isobolograms were chosen to display interactions graphically [2].

The potency ratio of Vec : 3-OH : 3,17-OH was 1:2:30 which is in agreement with others [3]. In the presence of a small dose (ED<sub>25</sub>) of Vec, the dose response curve of 3,17-OH was shifted significantly to the right. Figure 1 shows that the effect (ED<sub>50</sub>) produced by the combination of Vec and 3,17-OH Vec is represented by a point above the line joining points of equal effects (the ED<sub>50</sub> isobol) which suggests antagonism. The combined ED<sub>50</sub> of Vec and 3-OH Vec is on the ED<sub>50</sub> isobol, suggesting the effects of the latter drugs in combination to be simply additive.

Our results show that 3,17-OH Vec acts antagonistic to Vec. A partial agonist-antagonist action of 3,17-OH Vec which is a very weak neuromuscular blocking drug seems to be responsible for the above observations. Accumulation of this metabolite during long term administration of Vec to ICU patients might be an explanation for the development of resistance to Vec.

References :

- 1) Anesth. Analg. 1989;69:518-521
- 2) Anesth. Analg. 1988;67:1-8
- 3) Brit. J. Anaesth. 1985, 57, 789-795

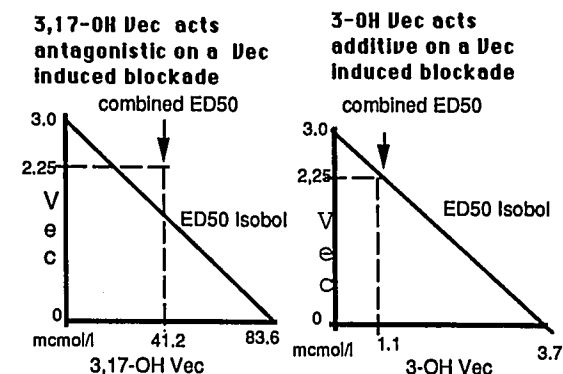


Figure one

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**Title:** ELIMINATION OF METOCURINE BY HEMOFILTRATION IN PATIENTS UNDERGOING CARDIOPULMONARY BYPASS  
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While pancuronium and vecuronium have been reported to be recovered in dialysate and hemofiltrate<sup>1,2</sup>, the elimination of muscle relaxants by these artificial means has not been systematically studied. Hemofiltration (HF), as often used during cardiopulmonary bypass (CPB), provides a useful clinical model to evaluate the elimination of a drug across dialysis membranes. In this study we investigated the elimination of the nondepolarizing muscle relaxant metocurine (MTC) by HF in patients undergoing CPB.

After receiving IRB approval and informed consent 8 patients with normal renal function undergoing elective cardiac surgery were studied. Anesthesia was induced with 50-100 µg.kg<sup>-1</sup> of fentanyl IV followed by MTC 0.3 mg.kg<sup>-1</sup> IV for tracheal intubation. An IV MTC infusion was simultaneously started at 0.04mg.kg<sup>-1</sup>.hr<sup>-1</sup> and continued throughout the remainder of the anesthetic. Hypothermic CPB was employed with hemodilution for 94.3±26.1 min. (mean ±SD). During CPB HF was employed with a Cobe hemofilter (Cobe Lab., Lakewood, CO) as required to maintain hematocrit between 24-26%. Typically, HF was used for 35 min during CPB with HF flow of approximately 200 ml.min<sup>-1</sup>. Plasma was obtained for MTC analysis from ports located before and after the HF. Metocurine concentrations were determined in plasma and urine by HPLC. Paired student t-test was used to compare plasma MTC concentrations with values of P<0.05 considered significant.

Plasma concentrations of MTC was significantly lower downstream from the HF compared to plasma concentrations obtained from HF inflow (table 1). Urine MTC concentration (mean±SD) during CPB was 0.941±0.41µg.ml<sup>-1</sup> (table 1). Urine volume during CPB was (mean±SD) 1218.6±1038ml. Hemofiltrate MTC concentrations were not detectable. Assuming an average HF blood flow of 200 ml.min<sup>-1</sup> for a duration of 30 min, approximately 1.55 mg of MTC would be eliminated by HF during CPB. In contrast, considering the mean urine volume and MTC concentrations observed in this report, approximately 1.1 mg of MTC would be renally eliminated during CPB.

Thus, it appears that MTC may be eliminated by HF, however, MTC binding to the hemofilter can not be ruled out. The use of HF should be considered in pharmacokinetic investigations during CPB.

Table 1. Plasma and urine MTC concentration (mean±SD, µg.ml<sup>-1</sup>)

Sample	[MTC]
Plasma HF Inflow	0.354±0.05
Plasma HF Outflow	0.096±0.06*
Urine during CPB	0.941±0.41

\*P<0.05 Plasma HF Outflow vs. Inflow

REFERENCES

1. Anesthesiology 69:996-997, 1988
2. Anesthesiology 72:566-570, 1990