TITLE: **EXTRAHEPATIC PROPOFOL METABOLISM: AN EVIDENCE.**

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Propofol (P) has a very high total body clearance, suggesting the existence of an extrahepatic metabolism (1). Metabolites are mainly excreted in urine; P glucuronide (Pg) represents approximatively 40 % of the administered dose. This study was designed to demonstrate the existence of an extrahepatic metabolism of P.

After informed consent and institutional approval, 9 patients undergoing orthotopic liver transplantation (OLT) (Group1), aged 41 ± 8 yrs (mean ±SD), weighing 58 ± 8 kg, were compared to 6 patients without liver dysfunction scheduled for an extrahepatic surgery (Group 2), aged 53 ± 10 yrs, weighing 71 ± 11 kg. In both groups, anesthesia was induced with thiopental 5 mg.kg-1 and maintained with a continuous infusion of fentanyl (10 µg.kg-1.h-1) and midazolam (50 µg.kg-1.h-1). Vecuronium was used for muscle relaxation. A single intravenous bolus dose of 0.5 mg.kg-1 of P was injected; in Group 1: 5 min after the beginning of the anhepatic phase; in Group 2: 1 h after the induction of anesthesia. Venous blood was sampled at 5, 10, 15, 20, 30, 40, 50 and 60 min after injection. During 1 h, urine samples were collected every 15 min. P levels in blood and urine were measured by HPLC with fluorescence detection. Pg was estimated in urine by using β glucuronidase and measuring the liberated P. P concentration time data were fitted to a three open compartment model. Results are expressed as mean ± SD. Differences in parameters between the 2 groups were assessed by Mann and Withney U test.

The figure illustrates the evolution of P blood levels in the two groups. No significant difference appears between the groups in the interpolated areas under the curves (AUC 0 ) and in the T1/2 β values (Table). Unchanged P was not found in urine. Pg was detected in the urine of the two groups (Table).

Our study shows that the anhepatic phase of OLT does not modify T1/2 β of P. Pg presence in urine of group 1 clearly demonstrates the extrahepatic metabolism of P, possibly due to lung contribution (2).

References: 1-Postgrad Med J, 61: 45-49,1985.
2- Anesthesiology, 65: A462, 1988.

| Table: mean ±SD | AUC (µg. l-1. h) | T1/2 β (h) | urinary Pg (µg) |
|---|---|---|---|
| Group 1 | 199.65 ± 44.95 | 0.71 ± 0.34 | 133.70 ± 106.10 |
| Group 2 | 124.24 ± 69.20 | 0.62 ± 0.21 | 123.30 ± 41.8 |
| U test | NS | NS | |

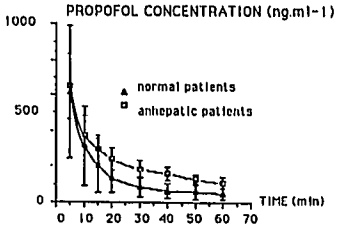


Figure: Time course evolution of P (mean ± SD).

## A330

TITLE: A COMPARISON OF NALMEFENE WITH NALOXONE AGAINST FENTANYL-PRODUCED ANTINOCICEPTION IN RATS

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Nalmefene, an analogue of naltrexone, is an antagonist of opiate receptor-modulated pharmacologic activity. A comparison of the narcotic antagonist activity of nalmefene and naloxone was conducted to assess the relative potencies of the two agents.

Male Sprague-Dawley rats were used in all experiments, which were approved by our Animal Care and Use Committee. All drugs were administered by i.v. injection.

Antinociception was assessed by the tail flick (TF) test. The tail was placed under a focused heat lamp and the latency to withdrawal was determined before (control) and after (treatment) drug injection. To prevent tissue damage, a maximum exposure may be only 10 seconds. The data are converted to the % maximal possible effect (%MPE) by:

$$\frac{\text{treatment latency - control latency}}{\text{10 sec - control latency}} \times 100$$

The $A_{50}$ (dose producing 50% MPE) was derived from linear regression of the log dose-response curve. Antagonistic potency was assessed by inhibiting the analgetic activity of a standard dose (0.0097 mg/kg) of fentanyl. Pretreatment TF latencies were determined for each group of animals which then received fentanyl and then a dose of nalmefene or naloxone; TF latencies were determined 1 min after each injection. The % antagonism was determined from:([% MPE(fentanyl) - % MPE(antagonist)]/[% MPE(fentanyl)])x 100. The $AD_{50}$ (median antagonistic dose) was determined from linear regression analysis of the dose-response curve. Duration of antagonism was measured by administering the $A_{50}$ dose of fentanyl at various time periods after the $AD_{99}$ dose of naloxone or nalmefene and determining the %MPE. The time point at which the response, as %MPE, was no longer significantly different from that of fentanyl plus saline alone (t-test) gave the duration of action.

Nalmefene was equipotent with naloxone as an opiate antagonist. Its AD50 was 0.011 mg/kg (95% C.L. 0.0021-0.052 mg/kg) whereas that of naloxone was 0.02 mg/kg (95% C.L. 0.0075-0.55 mg/kg). These values were not significantly different. The dose-response curves for nalmefene and naloxone were parallel. The duration of action of nalmefene was 540 min whereas that of naloxone was 180 min. When various doses of fentanyl were administered 1 min after the injection of the $AD_{50}$ dose of nalmefene or naloxone, both antagonists produced a parallel shift to the right of the fentanyl dose-response curve in the TF test (Table 1).

**Table 1:**

| | A50 (mg/kg) | | |
|---|---|---|---|
| Fentanyl Alone | 0.0097 | (0.0081 - 0.011) | |
| Fentanyl + Nalmefene | 0.051 | (0.028 - 0.093) | (5-Fold Shift) |
| Fentanyl + Naloxone | 0.079 | (0.0027 - 2.29) | (8-Fold Shift) |

The $A_{50}$ of fentanyl plus naloxone was not significantly different than that of fentanyl plus nalmefene.

Nalmefene and naloxone both reverse the antinociceptive effect of fentanyl, and are equipotent in this respect. Nalmefene also has 3 times the duration of action as naloxone against fentanyl when given by the i.v. route. The parallel shift in the fentanyl dose-response curves indicate that nalmefene, like naloxone, antagonizes the effect of fentanyl directly at the opiate receptor sites.