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Effect of a continuous epidural infusion of ropivacaine on CYP2D6 activity in surgical patients

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Background: Ropivacaine and one of its metabolites, PPX, inhibit CYP2D6 (an important drug metabolizing enzyme in the cytochrome P450 system) in human liver microsomes in vitro with K_i values of 5 μ M (1.4 mg/L) and 13 μ M (3.6 mg/L), respectively.

Aim: To investigate the effects of a continuous epidural infusion of ropivacaine of at least 50 hours on the CYP2D6 activity.

Methods: Thirteen ASA I-II patients aged 41-85 years (median 68 years), undergoing hip or knee replacement were included. All patients were caucasian and extensive metabolizers with respect to CYP2D6 activity, as determined by genotyping (poor and extensive metabolizers because of genetic polymorphism for CYP2D6). During the study patients were not allowed to use medication known to inhibit or being metabolized by CYP2D6 or drugs known to be strong inhibitors or inducers of CYP1A2 or CYP3A4, both being important enzymes for the metabolism of ropivacaine.

Before surgery an epidural bolus of 150 mg ropivacaine was given. After surgery, and provided the Bromage motor block score was ≤ 2 , a continuous epidural infusion of ropivacaine 2 mg/ml was started at a rate of 14 mL/h. In case of unacceptable motor or sensory block or adverse reactions, the infusion rate could be decreased to a minimal infusion rate of 10 mL/h.

The day before surgery and at 40 hours after the start of the epidural infusion patients received a single tablet of 10 mg debrisoquine (a marker for CYP2D6 activity). Following administration of debrisoquine urine was collected for 10 hours to determine debrisoquine (D) and 4-hydroxy-debrisoquine (4-OH-D) in order to calculate the metabolic ratio (MR). $MR = D/4-OH-D$ in 0-10 h urine. D and 4-OH-D levels were determined by a high performance liquid chromatography method. Peripheral venous plasma samples were collected immediately before and 5 and 10 hours after the second administration of D and total ropivacaine was determined by a Liquid Chromatography – mass spectrometry method (LC/MS) and free ropivacaine and free PPX were determined by LC/MS after ultrafiltration

Results: MR before and after epidural infusion of ropivacaine were 1.0 ± 1.0 (min-max 0.1-3.4) and 2.3 ± 2.2 (min-max 0.3-6.7). The Hodges Lehman Estimate of the ratio MR after/MR before administration of ropivacaine was 2.2 with a 95% Confidence interval 1.9-2.7 ($P < 0.001$).

Total and free plasma concentrations of ropivacaine and PPX were similar before and 5 and 10 hours after administration of debrisoquine. Mean \pm SD plasma levels 10 hours after intake of D were: total ropivacaine: 2.4 ± 1.0 ; free ropivacaine: 0.05 ± 0.02 ; total PPX: 1.0 ± 0.3 ; free PPX: 0.37 ± 0.15 .

Conclusion: Continuous epidural infusion of 20-28 mg/h ropivacaine for 50 h inhibits the activity of CYP2D6 in extensive metabolisers resulting in a 2-fold increase in the metabolic ratio of debrisoquine. However, none of the patients was converted into a functional poor metabolizer ($MR > 12.6$) and the effect on the metabolism of other drugs is not expected to be of any major clinical importance.