Study Design

This was a phase I, single center, open-label study. After stable anesthesia was achieved using alfentanil and propofol, rocuronium administration began at an initial infusion rate of 200 µg/kg/hour (note: recommended initial infusion rate for continuous infusion is 600 to 720 µg/kg/hour). It was then adjusted to maintain a stable T1 at 50% of the baseline value. After stabilization of neuromuscular block, dexmedetomidine was administered to achieve a steady concentration of 0.6 ng/mL using a computer controlled infusion pump. After 45 minutes of dexmedetomidine infusion, all infusions were stopped.

Results and Discussion

Statistical analysis was done to compare rocuronium concentrations prior to and 15, 30, and 45 minutes after initiation of dexmedetomidine infusion by a paired t-test. No statistically significant difference was found between the rocuronium concentrations immediately before the start of dexmedetomidine infusion and concentrations 15 and 30 minutes later. However, there was a significant difference for the comparison of pre-dexmedetomidine rocuronium concentrations and those 45 minutes later. It should be noted that the elapsed time from last change in rocuronium infusion rate until dexmedetomidine infusion began ranged from 10-24 minutes meaning that rocuronium with a terminal half-life of 71 minutes will not achieve new steady state concentrations within the 45 minutes of dexmedetomidine infusion. This is reflected in the small rise in rocuronium concentrations during the 45 minutes of dexmedetomidine infusion. The small but statistically significant difference between concentrations of rocuronium prior to dexmedetomidine infusion as compared to 45 minutes after the start of dexmedetomidine may be due to rocuronium not having achieved steady-state (1.66 versus 1.79 ng/mL).

The changes in neuromuscular block before and after dexmedetomidine infusion were small (6.6% in T_1%), clinically undetectable, and considered clinically unimportant by the investigator.

Table 1. Mean dexmedetomidine and rocuronium concentrations.

Time After Start of Dexmedetomidine Administration (minutes)	Dexmedetomidine Concentrations (ng/mL)	Rocuronium Concentrations (ng/mL)
0	0.002 ± 0.005	1.66 ± 0.29
15	1.03 ± 0.15	1.73 ± 0.37
30	0.96 ± 0.15	1.78 ± 0.43
45	0.94 ± 0.14	1.79 ± 0.41

Note: Lack of analytical assay validation data precludes the use of rocuronium pharmacokinetic information in the package insert.

IN VITRO METABOLISM

Study Type: *In Vitro* Metabolism and inhibition.

NDA: 21-038 **Submission Date**: 12/18/98 **Volume**: 1.49 **Protocol**: R&D/97/757

Objective:

To identify the hepatic cytochrome P450 proteins involved in the metabolism of [^{3}H]dexmedetomidine in human liver microsomes and human B-lymphoblastoid micosomes containing cDNA expressed cytochrome P450 proteins.

Conclusions:

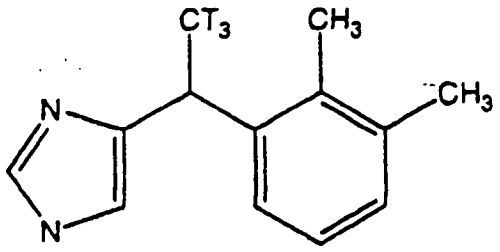
Based on the results from this study, it was concluded that the hydroxylation of dexmedetomidine to 3-hydoxy dexmedetomidine and H-3 is largely mediated by CYP2A6, although other CYP forms may also play an ancillary role. Evidence for the involvement of CYP2A6 included: 1) 8-methoxypsoralen, a CYP2A6-selective inhibitor, inhibited (41-59%) the hydroxylation to both products; 2) coumarin, a CYP2A6-selective substrate, inhibited (34%) the hydroxylation to 3-hydroxy dexmedetomidine; 3) hydroxylation was also observed with human B-lymphoblastoid microsomes containing cDNA-expressed CYP2A6; and 4) the hydroxylation of dexmedetomidine was inhibited (33%) by a CYP2A6 antibody. Inhibition by CYP2A6 selective inhibitors, including antibodies, was incomplete and may indicate the involvement of one or more other CYP isozymes in human liver microsomes. Furthermore, minimal inhibition (<20%) by selective inhibitors of CYPs other than CYP2A6, lend credence to speculation that more than one other CYP isozyme might me involved. Several other cDNA expressed CYPs were also capable of catalyzing the metabolism of dexmedetomidine to one or both major products indicating that other CYP isoforms (e.g., CYP1A2, CYP2E1, CYP2D6 and CYP2C19) may play a role in the hydroxylation of dexmedetomidine.

The dexmedetomidine IC_{50} values for inhibition of the various isoforms ranged from 0.2-3.3 μM for the inhibition of 1A1 (2.7 μM), 1A2 (2.0 μM), 2A6 (70 μM), 2C19 (3.3 μM), 2D6 (1.3 μM), 2E1 (2.2 μM), and 3A4 (0.65 μM). Since the plasma concentrations of dexmedetomidine at clinically relevant doses are very low (≤10 ng/mL; ≤0.04 μM) compared to the *in vitro* determined IC_{50} values, the possibility of an inhibitory effect of dexmedetomidine on the metabolism of coadministered drugs *in vivo* in humans appears to be unlikely. In a clinical interaction study, dexmedetomidine did not have any effect on the pharmacokinetics of midazolam, a CYP3A substrate. The lack of inhibitory effect is possibly due to very low plasma levels of dexmedetomidine (0.2-0.4 ng/mL) observed in this study, which are several fold lower than the in vitro determined IC_{50} values for CYP3A4 inhibition (0.65 μM; 110 ng/mL).

Experimental

Drugs

Dexmedetomidine was labeled with tritium, as shown in the figure below:



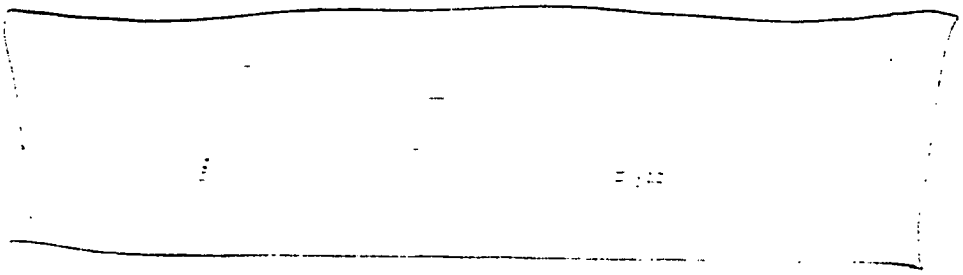
[^{3}H]Dexmedetomidine (Lot 55585-ST-108; 66 Ci/mmol; hydrochloric acid salt) was dissolved in ethanol and stored at -20°C. The radiochemical purity was greater than 97%. Unlabeled dexmedetomidine (Lot No. 031940-002) was combined with the labeled drug only for final incubations requiring concentrations greater than 0.05 µM.

Preparation of Liver Microsomes

Transplant quality human liver tissue was obtained from [redacted] was received at Abbott Laboratories within 24 hours of removal from the donor. Based on studies with microsomes containing cDNA expressed CYPs and given the potential role of CYP2D6 in the oxidative metabolism of dexmedetomidine, liver microsomes prepared from an extensive metabolizer (ID:1211961; male subject) and a poor metabolizer (ID:415961; male subject) of CYP 2D6 substrates were used in this study.

[redacted]

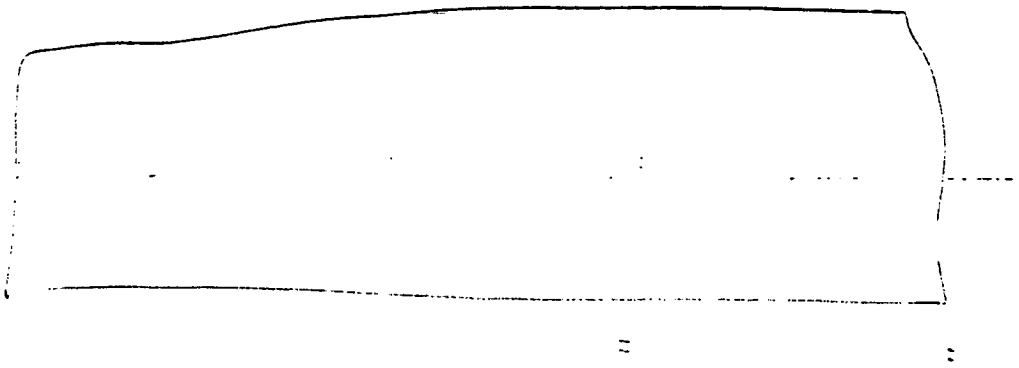
subsequently homogenized with [redacted] and the resultant homogenate was centrifuged [redacted] it was carefully



In Vitro Metabolism of [^{3}H]Dexmedetomidine

Assay System

In vitro incubations of [^{3}H]dexmedetomidine with human hepatic microsomes were performed at



Involvement of the CYP system in the metabolism of both compounds was assessed by omission of the NADPH and by the use of several CYP isoform selective inhibitors.

Identification of the Oxidative Metabolites of Dexmedetomidine Produced by Human Liver Microsomes

In vitro incubations of [^{3}H]dexmedetomidine with human hepatic microsomes for the

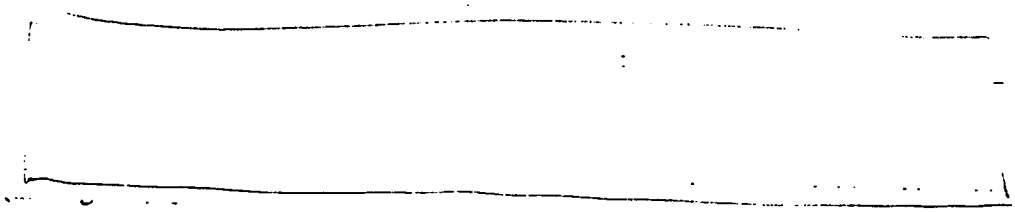


Table 3. IC_{50} values for inhibition of dexmedetomidine against the different cytochrome P450 isoforms.

Cytochrome P450 isoform	Substrate	IC_{50} (μM)
1A1	Ethoxyresorufin O-deethylase	2.7
1A2	Ethoxyresorufin O-deethylase	2.0
2A6	Coumarin 7-hydroxylase	70
2C19	S-mephenytoin 4-hydroxylase	3.3
2E1	Chlorzoxazone 7-hydroxylase	2.2
3A4	Testosterone 6β-hydroxylase	0.65
2D6	Dextromethorphan O-demethylase	1.8

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