TITLE: EVIDENCE FOR POLYMORPHIC OXIDATION OF ALFENTANIL IN MAN

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Introduction: Metabolic studies with the antihypertensive drug debrisoquine have revealed a subpopulation of poor hydroxylator phenotypes which had high drug blood levels and increased drug sensitivity. Poor hydroxylators of debrisoquine (up to 10% of some populations) also have impaired oxidation of phenacetin, metoprolol, phenytoin and other compounds. Phenacetin has been used to test for the debrisoquine type of genetic polymorphism.[1]

We had previously reported a healthy non-obese patient who had a markedly reduced clearance for alfentanil.[2] Our finding was not unique, as similar individuals had been found in three other pharmacokinetic studies of alfentanil. As alfentanil is metabolized primarily by oxidative O-demethylation and N-dealkylation, we tested the hypothesis that impaired alfentanil clearance is the result of an abnormal oxidative phenotype. In the present study our subject who had poor alfentanil clearance and controls were challenged with phenacetin, and two oxidative phenotypes were distinguishable.

Methods: The investigation was approved by the Institutional Human Studies Committee and informed consent was obtained. Each of four subjects received phenacetin 1 gm p.o. and plasma was obtained before the dose and at 1, 2, 4, 6, 8 and 24 hours after the dose. Urine was collected at 0-2, 2-4, 4-6, 6-8, 8-12, 12-16 and 16-24 hrs after the dose. Plasma and hydrolyzed (glucuronidase-sulfatase) urine was extracted into ethyl acetate and injected onto a gas chromatograph/ mass spectrometer as trimethylsilyl derivatives for quantitation of phenacetin and its major metabolite, acetaminophen. Deuterated acetaminophen was used as an internal standard. AUC (area under curve) for plasma phenacetin was obtained by Simpson's Rule, and clearance to acetaminophen (ratio of cumulative urinary acetaminophen excretion to the AUC of plasma phenacetin) was computed for each subject. Data are presented as mean ± SD.

	Phenotype PM (n=1)	Phenotype EM (n=3)
AUC-phenacetin ($ug \cdot min \cdot ml^{-1}$)	524	163 ± 58
Clearance to Acetaminophen ($ml \cdot min^{-1}$)	378	1821 ± 1329

Results: The data revealed three extensive metabolizers (EM) and one poor metabolizer (PM) of phenacetin. The PM subject also had impaired clearance of alfentanil.[2] Plasma phenacetin concentrations were much higher for the PM subject (3-fold greater AUC). There was a 4.8-fold greater clearance of phenacetin to acetaminophen in the EM subjects, indicating the difference in acetaminophen excretion was due to a difference in metabolic conversion from phenacetin.

Discussion: This study demonstrated that phenacetin hypometabolism occurred in the same subject who demonstrated alfentanil hypometabolism. The variation in plasma phenacetin levels and clearance to acetaminophen were in accord with EM/PM ratios in similar studies[1], suggesting that alfentanil oxidation exhibits the debrisoquine type of genetic polymorphism. This has important clinical implications. Up to 10% of patients are known to have debrisoquine hypometabolism and, therefore, would have reduced alfentanil clearance. This in turn would lead to prolonged elevation of plasma levels of alfentanil with either infusion or bolus regimens.

References:
1. Sloan TP et al: Polymorphism of carbon oxidation of drugs and clinical implications. Br Med J 2: 655-657, 1978.
2. McDonnell TE et al: Nonuniformity of alfentanil pharmacokinetics in healthy adults. Anesthesiology 57: A236, 1982.