TITLE: AIRWAY RESPONSES TO ARACHIDONIC ACID AFTER THROMBOXANE SYNTHETASE BLOCKADE BY CGS 13080

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Introduction. The fatty acid precursor arachidonic acid (AA), is converted by most organ systems including the lung, into primary prostaglandins (PG), thromboxane A_2 (TxA_2) and prostacyclin (PGI_2) via the microsomal cyclooxgenase system. TxA_2 has potent smooth muscle stimulating and platelet aggregating activities. The present study was done to assess the effects of TxA_2 on the airways and systemic circulation of the cat.

Methods. Twenty six mongrel cats, unselected as to sex were anesthetized, paralyzed, and mechanically ventilated with room air. Transpulmonary pressure (P_{TP}) was measured via a transducer coupled between the tracheal tube and a pleural cannula inserted in the chest. Tidal airflow (V_T) was measured by coupling a differential transducer to a pneumotachograph. Tidal volume, lung resistance (R_L), and dynamic compliance (C_{dyn}) were calculated on a breath-to-breath basis from P_{TP} and V_T signals by a Hewlett-Packard respiratory analyzer. Catheters were advanced from a femoral artery for recording aortic blood pressure (P_{Ao}) and from a femoral vein for IV administration of drugs. Control responses to random doses of AA and U-46619 (a TxA_2 receptor agonist) were obtained in all animals. CGS 13080, 10mg/kg was given. Airway responses and aortic pressure responses were recorded following repeated random doses of AA and U-46619. Sodium meclofenamte 2.5 mg/kg, a cyclooxygenase inhibitor was administered and responses to AA & U-46619 again recorded. Values of all parameters are expressed as mean ± standard error.

Results. All control IV doses of AA and U-46619 produced dose dependent bronchoconstriction as measured by increases in P_{TP} (Figure 1). Bronchoconstriction involved both central airways, as measured by increases in R_L, and peripheral airways, as measured by decreases in C_{dyn}. Responses to U-46619, the TxA_2 receptor agonist, were not inhibited by either CGS 13080 or meclofenamate (Figure 2). Airway responses to low dose AA (300mg) were diminished 65 to 75% by CGS 13080. Cyclooxygenase inhibition with meclofenamate consistently blocked AA induced changes in P_{TP}, R_L, and C_{dyn} by 71-88%. AA produced dose-dependent decreases in P_{Ao} which were not blocked by CGS 13080, but which were significantly blocked by meclofenamate. U-46619 produced a brief, dose-dependent, systemic pressor response that was temporally related to increases in R_L, and that was unaffected by either CGS 13080 or meclofenamate.

Discussion. Cyclooxgenase blockade will prevent the bronchoconstriction elicited by AA. Selective TxA_2 synthetase inhibitors have shown the relative contribution of TxA_2 versus the classical PG's. CGS 13080 behaves as a specific TxA_2 synthetase inhibitor in vitro based on microsomal studies conducted from this lab. Furthermore, it did not attenuate the bronchoconstrictive effects of U-46619, indicating CGS is not a receptor antagonist.

Our results suggest that the classical PG's have more peripheral than central airway activity as the AA induced changes in C_{dyn} were not as attenuated by CGS 13080 as were the changes in R_L. AA produced a marked systemic vasodepressor response, most likely secondary to PGI_2. The AA-induced depressor response was preserved following CGS 13080 indicating that it does not interfere with prostacyclin synthetase. TxA_2 synthetase inhibitors may be useful in clinical states associated with increased TxA_2 such as: pulmonary hypertension associated with endotoxemia and ARDS, as well as acute bronchoconstrictive disorders and thromobotic states. In summary the TxA_2 synthetase inhibitors CGS 13080 effectively blocked the bronchoconstrictive effects of AA while preserving its systemic vasodepressor responses.