Pharmacokinetics of Sulindac in ESRD

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Dear Sir

We would like to express our congratulations to Nesher et al. [1] on their carefully designed prospective study revealing a reduction in the incidence of azotemia and hyperkalemia with the use of sulindac compared with indomethacin. However, we also offer a mild objection to their conclusion that their findings indicate a preference for sulindac over indomethacin in patients with renal insufficiency. We have recently concluded a study of sulindac and have found that the active metabolite, sulindac sulfide, is markedly reduced in patients with renal insufficiency when compared to normal controls.

Six normal volunteers and six patients with end-stage renal disease (ESRD) received one 300-mg tablet of sulindac after an 8-hour fast in an effort to study the pharmacokinetics in ESRD. Blood samples were drawn prior to the dose and 20 additional times over the next 60 h. Analyses were performed for sulindac, sulindac sulfide, and sulindac sulfone in serum. Protein-binding studies were performed in plasma. The AUC and AUMC for sulindac in both metabolites were calculated by linear trapezoidal rule method. The apparent body clearance (CL/F) of sulindac was determined by dividing the dose by the AUC. A statistically significant difference was found in the plasma concentration (fig. 1), AUC, between normal subjects and patients with ESRD for the sulindac metabolite which is thought to be clinically active.

Unlike most other drugs which are normally excreted through the kidney, sulindac and its active metabolite, sulindac sulfide, experience a decrease in serum levels in renal insufficiency when compared to normal controls. Therefore, while renal prostaglandins may not be inhibited in patients with renal insufficiency this may be merely a function of a subtherapeutic plasma level of the active metabolite of sulindac. Therefore, while sulindac may

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Fig. 1. Plasma concentrations of sulindac, sulindac sulfide and sulindac sulfone in controls (O) and patients with ESRD (●).

not be harmful in renal insufficiency, it also may not be therapeutic with conventional doses. Before Dr. Nesher may be justified in choosing sulindac over other nonsteroidal anti-inflammatory drugs because of reduced toxicity, it must be proven or not sulindac can be of any therapeutic benefit at conventional doses in renal insufficiency patients, when its active metabolite form, sulindac sulfide, is only present in negligible quantities.

Reference