THE EFFECT OF pH ON THE BUCCAL ABSORPTION AND RENAL EXCRETION OF INDOMETHACIN

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Indomethacin is an antiinflammatory drug which has been widely used over the past ten years with considerable benefit to many arthritic patients. After an oral dose the drug is completely absorbed and subsequently eliminated, mainly as the glucuronide and partly as the unchanged drug, in the urine; some of the drug is also recovered in the bile as glucuronide. Probenecid has been found to inhibit the renal excretion of indomethacin in healthy volunteers: the peak blood concentrations of indomethacin 4 hours after administration were about 50% higher after probenecid treatment (Skeith et al 1968). However, probenecid did not appear to inhibit the renal excretion of the unchanged drug, although it did influence the non-renal clearance probably the biliary excretion, of indomethacin (Baber et al 1978). Recently, we have also shown that indomethacin itself does not alter the clearance of creatinine (hence, renal function) in volunteers and in patients on long term treatment with the drug (Baber et al 1980).

Although indomethacin is a weakly acidic compound and has a pKa of 4.5, very little is known of the influence of urinary pH on the renal elimination of the unchanged drug. A preliminary study on the effect of pH on the buccal absorption of indomethacin indicated that the amount absorbed increased as the pH of the buccal medium decreased. This effect was further studied in three volunteers (one female and two male subjects) between pH 3.6 and 8.

The urinary recovery of the unchanged drug in five additional healthy male volunteers was investigated under conditions of uncontrolled and controlled, acidic and alkaline, urinary pH according to a procedure previously described for pethidine (Chan, 1979). Each subject, after an overnight fast, ingested two "Indocin" capsules (25mg) with 200ml of water. Plasma samples were collected at 0, 1, 2, 3, 4, 6, 8, 10, 12, 14 and 24 hours, and bulked urine samples at 0, 1.5, 2.5, 3.5, 5, 7, 9, 11, 13 and 24 hours after dosing. (The protocol of these studies were seen and approved by the Regional Ethical Committee.) Concentrations of indomethacin in mouth washes after buccal absorption tests were measured by a modified spectrofluorometric technique (Holt & Hawkins 1965) while plasma and urine indomethacin were determined by a gas chromatographic procedure (Sibeon et al 1978).

The results of the buccal absorption tests showed that $69.8 \pm 8.0\%$ and $1.3 \pm 0.3\%$ of indomethacin was absorbed through the buccal mucosa at pH 3.6 and 8 respectively. The urinary recovery of unchanged indomethacin is highest at alkaline pH ($16.8 \pm 7.4\%$) and lowest at acidic pH ($6.7 \pm 1.4\%$); the recovery under uncontrolled urinary pH is $8.7 \pm 1.4\%$. Although urinary pH influences the renal elimination of unchanged indomethacin, there is no apparent change in plasma levels of the drug under the three conditions of urinary pH. In contrast to previous observations (Skeith et al 1968), it seems unlikely that physiological changes in urinary pH during long-term treatment of arthritic patients will influence the overall pharmacokinetics of indomethacin.

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