

Peak plasma concentration of rhein was reached 15-30 minutes after dosing. Binding of rhein to plasma proteins is >99%; area under the curve (AUC) is 20.9 mg/l.h after a single dose (50 mg) and 28.8 mg/l.h after repeated doses (50 mg/day for 5 days).

2. Protein binding

Rhein, a weak acid drug (pKa = 4-4.5); is present essentially in its ionized form in the plasma. Plasma protein-binding of rhein was almost 100% according to a radiochemical studies in 4 healthy volunteers (Fisher, 1994; Lang, 1994). Furthermore, consistent with subsequent clinical studies showing no drug interactions, bound rhein was not displaced by drugs that might be administered concomitantly, such as anticoagulants, anticonvulsants or non-steroidal anti-inflammatory drugs (Barre, 1992) as demonstrated by studies in vitro.

3. Metabolism and elimination

Diacerein is hydrolysed to rhein, the active metabolite, rapidly upon oral administration and before entering the systemic circulation as seen in figure 5. After a single 50 mg dose, 19.6±11.3% of the metabolites were excreted via the urine in the form of non-conjugated rhein while 62.7±13.5% was in the form of glucuroconjugated rhein and 18.6±5.6% in the form of sulphuronoconjugated rhein (Louchahi et al., 1991).