Clinical Pharmacokinetics of Diacerein

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Abstract

Diacerein is a drug for the treatment of patients with osteoarthritis. This drug is administered orally as 50mg twice daily. Diacerein is entirely converted into rhein before reaching the systemic circulation. Rhein itself is either eliminated by the renal route (20%) or conjugated in the liver to rhein glucuronide (60%) and rhein sulfate (20%); these metabolites are mainly eliminated by the kidney.

The pharmacokinetics characteristics of diacerein are about the same in young healthy volunteers and elderly people with normal renal function, both after a single dose (50mg) or repeated doses (25 to 75mg twice daily). Rhein kinetics after single oral doses of diacerein are linear in the range 50 to 200mg. However, rhein kinetics are time-dependent, since the nonrenal clearance decreases with repeated doses. This results in a moderate increase in maximum plasma concentration, area under the plasma concentration-time curve and elimination half-life. Nevertheless, the steady-state is reached by the third administration and the mean elimination half-life is then around 7 to 8 hours.

Taking diacerein with a standard meal delays systemic absorption, but is associated with a 25% increase in the amount absorbed. Mild-to-severe (Child Pugh’s grade B to C) liver cirrhosis does not change the kinetics of diacerein,
whereas mild-to-severe renal insufficiency (creatinine clearance <2.4 L/h) is followed by accumulation of rhein which justifies a 50% reduction of the standard daily dosage.

Rhein is highly bound to plasma proteins (about 99%), but this binding is not saturable so that no drug interactions are likely to occur, in contrast to those widely reported with nonsteroidal anti-inflammatory drugs. Except for moderate and transient digestive disturbances (soft stools, diarrhoea), diacerein is well tolerated and seems neither responsible for gastrointestinal bleeding nor for renal, liver or haematological toxicity.

Articular cartilage degradation is a common feature of many rheumatic diseases with clearly different aetiologies, such as osteoarthritis or chronic rheumatoid arthritis. The physiopathology of this degradation is rather complex and multifactorial, but it is well known today that inflammatory and immunogenic processes greatly contribute to it. However, a truly satisfactory therapy is still lacking and clinicians must resort to symptomatic treatments. Among them, we find nonspecific drugs [analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs)] and drugs claiming specific anti-osteoarthritic activity, such as chondroitin sulfate, avocado and soya extracts, hyaluronic acid and diacerein.

First released in Italy during the 1970s, diacerein has more recently been marketed in France (approved in 1992) and new approvals are expected or already obtained in other countries. As illustrated in figure 1, diacerein is the di-acetylated derivative of rhein, a molecule with an anthraquinonic ring.

Rhein is actually the active metabolite of diacerein. Rhein exerts anti-inflammatory properties through inhibition of interleukin-1, a cytokine highly involved in the degenerative process of cartilage. This inhibition has been confirmed in fundamental research based either on animal models of inflammation or on chondrocyte cell cultures.[11]

Diacerein shows no effect on prostaglandin synthesis, either in experimental studies[2,3] or in patients.[4] Therefore, diacerein can be considered as a slow-acting anti-arthritic drug not belonging to the NSAIDs that may interfere with the pathological course of osteoarthritis.

A clinical benefit with oral diacerein 50mg twice daily has been shown in clinical trials of less than 6 months’ duration.[1,5-7] In addition, a 3-year multicentre, randomised, placebo-controlled trial involving more than 500 patients with osteoarthritis is still ongoing and will provide important information for clinical practice.[8]

In this review, we describe the clinical pharmaco-

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**Fig. 1.** Chemical formulae of diacerein and rhein.