Clinical Pharmacokinetics of Sulindac
A Dynamic Old Drug

Neal M. Davies¹ and M. Scott Watson²

¹ Faculty of Medicine, Department of Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, Canada
² Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

Summary

Sulindac is a nonsteroidal anti-inflammatory drug (NSAID) of the indene acetic acid class. The absorption of sulindac is rapid when given orally. Sulindac is reversibly metabolised to sulindac sulphide which has anti-inflammatory and analgesic properties and is irreversibly metabolised to sulindac sulphone which has been suggested to possess antiproliferative effects against tumours. Sulindac and its sulphide and sulphone metabolites bind extensively to plasma albumin.

Sulindac is eliminated following bio-transformation; sulindac and sulindac sulphone and their respective glucurooconjugated metabolites are excreted in urine; however only a small amount of the sulindac sulphide metabolite is eliminated in urine. Following long term twice daily administration both sulindac and its metabolites accumulate in plasma.

Both patients with cirrhosis and the elderly demonstrate elevated concentrations of all species upon long term sulindac administration as compared with a single dose. The disposition of sulindac and its metabolites may be tied to renal function. In end-stage renal disease, increased free fractions of all species and accumulation of the sulphide and sulphone metabolites, and to a lesser extent
Sulindac \{\(Z\)-5-fluoro-2-methyl-1-[4-(methylsulphinyl)phenyl]methylene]-1H-indene-3-acetic acid\} is a nonsteroidal anti-inflammatory drug (NSAID) structurally similar to indomethacin. Sulindac is a pro-drug with the \(p\)-methylsulphinyl group converted to the sulphide metabolite which is a potent inhibitor of prostaglandin synthesis\(^{11}\) (fig. 1).

Therapeutic doses of sulindac have proven to be equi-efficacious compared with other commonly used NSAIDs in the short term alleviation of pain and in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gouty arthritis.\(^{12}\) Sulindac also demonstrates tocolytic properties and has been used effectively in the treatment of preterm labour.\(^{3,4}\) In addition, sulindac, which is a potent inhibitor of aldose reductase and sorbitol formation,\(^{5-7}\) can prevent alternations in permeability of the blood-retinal barrier,\(^{8}\) and consequently sulindac has been used topically in the treatment of diabetic senile cataracts.\(^{19}\) Finally, there are now numerous studies and case reports which say that sulindac is able to suppress the development of premalignant colonic polyps in patients with familial adenomatous polyposis (FAP)\(^{10-14}\) and can also inhibit mammary carcinogenesis in rats.\(^{15}\)

Gastrointestinal complications which extend from the oesophagus to the large intestine are the most common adverse effect of sulindac,\(^{16-19}\) but renal dysfunction,\(^{20-22}\) hepatic dysfunction,\(^{23}\) pancreatitis,\(^{24}\) hypersensitivity reactions,\(^{25}\) haemolytic anaemia,\(^{26}\) aseptic meningitis,\(^{27}\) Stevens-Johnson syndrome\(^{28}\) and the exacerbation of Parkinson disease\(^{29}\) also occur.

A general review article is available which deals with the pharmacological properties and therapeutic uses of sulindac,\(^{2}\) but that article does not discussed in detail the unique features ascribed to the clinical pharmacokinetics of sulindac. In this article the clinical pharmacokinetics of sulindac are updated and reviewed.

---

1. Analytical Methods

Several analytical methods are available for the quantitative analysis of sulindac in biological specimens. The earlier methods employed isotope dilution radioimmunoassay,\(^{30}\) computerised mass spectral assay,\(^{31}\) differential pulse polarography\(^{32}\) and thin layer chromatography.\(^{33}\) More recently, analysis has been accomplished using reverse-phase radial compression chromatography which can...

---

**Fig. 1.** Pathways of sulindac metabolism. * denotes the chiral centre.