ANTI-INFLAMMATORY DRUGS, NONSTEROIDAL (Systemic)

Indomethacin¾Indometacin.

Accepted

Rheumatic disease (treatment), such as

Arthritis, rheumatoid¾Diclofenac, 23, 158 diflunisal, 24, 165, 219 fenoprofen, 26, 27, 186, 187 flurbiprofen, 29, 126, 144, 169, 220 ibuprofen, 31, 38, 139, 181, 182, 183, 222 indomethacin, 32, 33, 175, 176 ketoprofen, 35, 36, 205, 206, 207 meclofenamate, 37, 178 nabumetone, 210, 211 naproxen, 1, 39, 40, 41, 142, 188, 189 oxaprozin, 163 phenylbutazone * , 42 piroxicam, 44, 45, 167, 168 sulindac, 46, 47, 160, 223 tenoxicam, 180 tiaprofenic acid, 48, 213 and tolmetin 49, 50, 215, 216 are indicated for the treatment of acute or chronic rheumatoid arthritis.

Osteoarthritis¾Diclofenac, 23, 156, 158 diflunisal, 24, 25, 165, 219 etodolac, 177 fenoprofen, 26, 27, 186, 187 flurbiprofen, 29, 126, 144, 169, 220 ibuprofen, 31, 78, 139, 181, 182, 183, 222 indomethacin, 32, 33, 175, 176 ketoprofen, 35, 36, 205, 206, 207 meclofenamate, 37, 178 meloxicam, 320 nabumetone, 211 naproxen, 1, 39, 40, 41, 142, 188, 189 oxaprozin, 163 phenylbutazone * , 42 piroxicam, 44, 45, 167, 168 sulindac, 46, 47, 160, 223 tenoxicam, 180 tiaprofenic acid, 48, 213 and tolmetin 49, 50, 215, 216 are indicated for relief of acute or chronic osteoarthritis.

Ankylosing spondylitis¾Diclofenac *, 58, 158 [diflunisal] * , 233 [fenoprofen] * , 233 [flurbiprofen] , 29, 126, 169, 220 [ibuprofen] * , 233 indomethacin, 32, 33, 175, 176 [ketoprofen] , 36, 206, 207 naproxen, 1, 39, 40, 41, 142, 188, 189 phenylbutazone, 42, 43 [piroxicam] , 45, 168 sulindac, 46, 47, 160, 223 tenoxicam, 180 and [tolmetin] 50, 216 are indicated for relief of acute or chronic ankylosing spondylitis.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to one of the nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ketorolac, and NSAIDs no longer commercially available (such as oxyphenbutazone, suprofen, and zomepirac) may be sensitive to any of the other NSAIDs also.
NSAIDs may cause bronchoconstriction or anaphylaxis in aspirin-sensitive asthmatics, especially those with aspirin-induced nasal polyps, asthma, and other allergic reactions (the "aspirin triad"").
Patients with bronchospastic reactions to aspirin may be desensitized to this effect by administration of initially small and gradually increasing doses of aspirin. Desensitization must be carried out by physicians who are experienced with the technique, in a facility having personnel, equipment, and medications immediately available for treatment of any adverse reaction to the medication (especially anaphylaxis or severe bronchospasm). Desensitization to aspirin also desensitizes the patient to other NSAIDs. However, unless aspirin or another NSAID is then administered on a daily basis, sensitivity to these medications redevelops within a few days. 15

Carcinogenicity

Diclofenac¾ No oncogenic potential was demonstrated with diclofenac sodium in a 2-year carcinogenicity study in male mice given up to 0.3 mg per kg of body weight (mg/kg) (0.9 mg per square meter of body surface area [mg/m 2]) per day or in female mice given up to 1 mg/kg (3 mg/m 2) per day.

Diflunisal¾ No effect on the incidence or type of neoplasia was found in a 105-week study in rats 24, 219 given up to 40 mg/kg per day (approximately 1.3 times the maximum recommended human dose [MRHD]) or in long-term studies in mice given up to 80 mg/kg per day (approximately 2.7 times the MRHD). 219

Etodolac¾ No carcinogenicity was demonstrated in mice or rats receiving up to 15 mg/kg per day (corresponding to 45 mg/m 2 for mice and 89 mg/m 2 for rats) for 2 years or 18 months, respectively. 177

Floctafenine¾ No effect on the incidence of neoplasia was found in studies in CD-1 mice receiving up to 240 mg/kg per day. 28

Flurbiprofen¾ No evidence of carcinogenicity was found in an 80-week study in mice receiving up to 14 mg/kg per day or in a 2-year study in rats receiving up to 12 mg/kg per day for 32 weeks, then up to 5 mg/kg per day thereafter. 144

Indomethacin¾ No evidence of carcinogenicity was found in studies in mice receiving up to 1.5 mg/kg per day for 62 to 88 weeks or in studies in rats receiving up to 1.5 mg/kg per day for 73 to 110 weeks. 32, 176

Tumorigenicity

Diclofenac¾ No tumorigenicity was demonstrated in studies in rats receiving up to 2 mg/kg per day (approximately the recommended human dose). 119 Although there was a slight increase in benign mammary fibroadenomas in female rats given 0.5 mg/kg (3 mg/m 2) per day, the increase was not significant. 158

Flurbiprofen¾ No tumorigenicity was demonstrated in a 2-year study in rats receiving up to 12 mg/kg per day for 32 weeks, then up to 5 mg/kg per day. 29

Indomethacin¾ No tumorigenicity was demonstrated in an 81-week study in rats receiving up to 1 mg/kg per day. 32, 176

Ketoprofen¾ No tumorigenicity was demonstrated in studies in rats receiving 6 mg/kg (36 mg/m 2) per day for 81 weeks or lower doses for 104 weeks. 205

Nabumetone¾ No tumorigenicity was demonstrated in 2-year studies in mice and rats. 211

Mutagenicity

Indomethacin¾ No mutagenic activity was demonstrated in in vitro tests (Ames test or E. coli , with or without metabolic activation) or in in vivo tests (host-mediated assay, sex-linked recessive lethals in Drosophila , and micronucleus test in mice). 32, 176

Ketoprofen¾ No mutagenic activity was demonstrated in the Ames test. 205

Pregnancy/Reproduction

Fertility¾Diclofenac¾ No impairment of fertility was demonstrated in reproduction studies in rats Indomethacin¾ No impairment of fertility was demonstrated in a 2-generation reproduction study in mice or in a 2-litter reproduction study in rats receiving up to 0.5 mg/kg per day. 32, 176

Indomethacin:

In addition to the adverse effects in animal studies described above, administration of indomethacin to pregnant women during the third trimester has caused closure of the ductus arteriosus, inhibition of platelet function resulting in bleeding, renal function impairment or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes in the fetus. 176

Breast-feeding

Indomethacin¾ Indomethacin is distributed into breast milk. 175, 176 Risk-benefit must be considered because convulsions were reported in one breast-fed infant whose mother received 200 mg of indomethacin per day, of which 0.5 to 2 mg per day was distributed into the breast milk.

Pediatrics

Ibuprofen¾ Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of ibuprofen in children 6 months of age or older. 139, 183 Safety and efficacy in infants younger than 6 months of age have not been established. 139, 183

Indomethacin¾ Although appropriate studies have not been done in the pediatric population, no pediatrics-specific problems have been documented to date (with the immediate-release capsule or oral suspension dosage form; the extended-release dosage form is not recommended for pediatric patients). 130, 176 However, because of indomethacin"s toxicity, it is recommended that its use be limited to patients unresponsive to (or intolerant of) other antirheumatic agents, 32, 176 that the patient be carefully monitored (especially for the presence of infection), and that the recommended pediatric doses not be exceeded. 32

Geriatrics

Indomethacin¾ In addition to the increased risks of therapy with any NSAID as described above, geriatric patients are more likely to develop adverse CNS effects, especially confusion, while taking indomethacin.

Ketoprofen¾ Studies have shown that protein binding and clearance of ketoprofen may be reduced, Platelet count

(may be decreased)