

The Anti-Inflammatory, Analgesic and Antipyretic Activity of Nimesulide in Experimental Models

G.P. Velo

Institute of Pharmacology, University of Verona, Verona, Italy

Summary

Nimesulide, a nonsteroidal anti-inflammatory drug (NSAID) chemically different from other drugs of this class, is a 4-nitro-2-phenoxy-methanesulfonanilide, with a sulfonanilide as the acidic group. The anti-inflammatory activity of nimesulide has been demonstrated in a number of widely used experimental models of inflammation such as carrageenan-induced paw oedema in rats, Freund's complete adjuvant-induced arthritis in rats, and UV-induced skin erythema in guinea-pigs.

The analgesic activity of nimesulide has been demonstrated in the Randall-Selitto test in rats and in the writhing test after intraperitoneal injection of phenylquinone in mice. Nimesulide also reduced the hyperthermia induced in rats by subcutaneous injection of yeast.

Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) that is chemically different from other drugs of this class. It is a 4-nitro-2-phenoxy-methanesulfonanilide, with a sulfonanilide as the acidic group.

1. Anti-Inflammatory Activity of Nimesulide

The anti-inflammatory activity of nimesulide has been demonstrated in a number of widely used experimental models of inflammation. These include the oedema produced in the hind paw of rats by the subplantar injection of carrageenan, the erythema produced in guinea-pig skin by UV irradiation, and the polyarthritis produced in rats by the intradermal injection of Freund's complete adjuvant.

1.1 Inhibition of Carrageenan-Induced Rat Paw Oedema

Nimesulide inhibited the swelling of the rat paw induced by carrageenan at oral doses as low as 0.3 mg/kg. The regression line is shown in figure 1. The oral ED₅₀ (dose producing a 50% inhibition of the swelling) in this assay was calculated from these data to be 1.99 mg/kg (fig. 1).

When administered at pretreatment intervals ranging from 15 minutes to 12 hours, nimesulide 1.5 mg/kg produced a significant inhibition of carrageenan-induced oedema of the rat paw at all times except the 3-hour pretreatment interval. The 3-hour value may be spurious or might relate to recirculation (e.g. enterohepatic) of the compound (fig. 2) [data on file, Helsinn].

In a comparative study, nimesulide was approximately 15 times more potent than phenylbutazone in inhibiting carrageenan-induced oedema of the rat paw. ED₅₀ values for nimesulide

and phenylbutazone were 1.7 mg/kg and 30 mg/kg, respectively (data on file, Helsinn).

Böttcher et al. (1987) found that nimesulide was as potent as indomethacin, diclofenac sodium and piroxicam in the carrageenan-induced rat paw assay, while Swingle and Moore (1984) estimated the potency of nimesulide after oral administration to be approximately 120 times that of aspirin and 3 times that of indomethacin in this test.

1.2 Inhibition of UV-Induced Erythema in Guinea-Pig Skin

Nimesulide inhibited the erythema induced in guinea-pig skin by UV irradiation. The oral ED₅₀ in this assay (95% confidence limits) was calculated to be 1.4 (1.2 to 3.1) mg/kg (data on file, Helsinn).

In a comparative study, Swingle and Moore (1984) found that nimesulide was approximately 4 times more potent than indomethacin in inhibiting UV-induced erythema of guinea-pig skin.

1.3 Reduction of Adjuvant-Induced Arthritis in Rats

Nimesulide administered orally on days 14, 15, 16 and 17 reduced the swelling of the hind paws and prevented loss of bodyweight in rats with established adjuvant-induced arthritis. At all doses

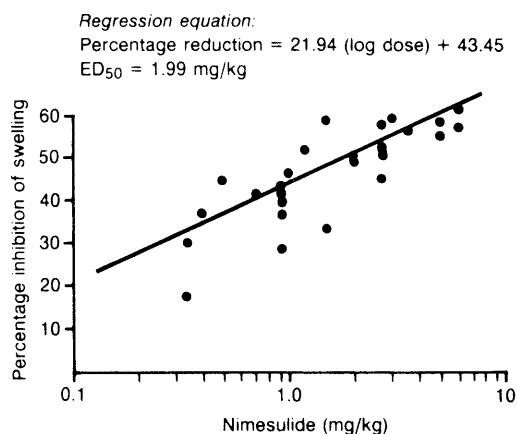


Fig. 1. The effect of an oral dose of nimesulide on the carrageenan-induced oedema of the rat paw.

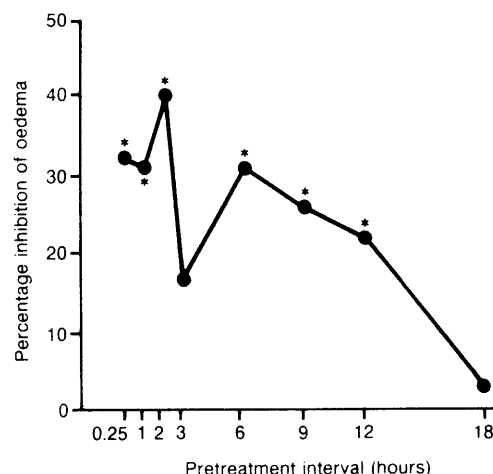


Fig. 2. Effect of varying the time of administration of nimesulide (1.5 mg/kg) on the inhibition of carrageenan-induced oedema of the rat paw. Mean values indicated by an asterisk (*) are significantly different ($p < 0.05$) from the control group (drug vehicle-treated) mean for that time interval. Ten rats were used to establish each mean value.

used (range 0.67 to 18 mg/kg), its administration not only prevented further increases in the volume of the arthritic paws but also reduced the pre-existing volume (data on file, Helsinn).

The effects of nimesulide and phenylbutazone on established adjuvant-induced arthritis were compared in one study. Doses of 0.2 mg/kg were effective in preventing a further increase in the volume of the arthritic paws. Nimesulide also produced a beneficial effect on the bodyweight of rats and it appeared to be at least 10 times more potent than phenylbutazone (data on file, Helsinn).

In another study, Böttcher et al. (1987) found that the ED₄₀ value of nimesulide in developing and established adjuvant-induced arthritis in rats was similar to those of indomethacin, diclofenac sodium and piroxicam.

1.4 Activity in Other Experimental Models

In the cotton pellet-induced granuloma assay, nimesulide at doses of 10 and 30 mg/kg/day did not significantly affect the dry weight of the granuloma or the wet weight of the adrenals or thymus.

However, hydrocortisone acetate (3.3 and 10 mg/kg/day) reduced the weight of these 3 tissues (data on file, Helsinn).

When administered at oral doses of 15 mg/kg, nimesulide had no effect on the swelling of the rat paw induced by formaldehyde, dextran, or serotonin. In contrast, cyproheptadine antagonised the oedematous response in the rat paw to injection of dextran or serotonin. Formaldehyde, dextran and serotonin are irritants which, in general, produce oedemas that are nonselective for NSAIDs (data on file, Helsinn).

1.5 Local Anti-Inflammatory Activity

Nimesulide inhibited carrageenan-induced oedema of the rat paw when administered locally at doses of 1, 2 or 4 mg/paw. Phenylbutazone also inhibited the oedema when administered by this route (data on file, Helsinn).

When applied topically to the hind paws of rats with established arthritis, nimesulide produced a significant reduction in the size of these paws. This effect occurred using either an acetone-ethanol solution of the compound or a suspension in 'Plastibase'. Systemic absorption of the compound must have occurred, since the contralateral nontreated paws were also reduced in size (data on file, Helsinn).

Nimesulide applied topically as a 3% ointment did not delay the erythema produced in guinea-pig skin by UV irradiation, and was ineffective in either hydrophilic or hydrophobic vehicles and whether applied before or after exposure of the skin to UV light. In contrast, indomethacin was very effective in inhibiting this reaction (data on file, Helsinn).

2. Analgesic and Antipyretic Activity of Nimesulide

2.1 Inhibition of the Writhing Responses

At doses of 5 and 20 mg/kg of nimesulide, the inhibition of phenylquinone-induced writhing in mice achieved statistical significance using the t-test, while doses of 1.25 mg/kg had no inhibitory effect. Similar experiments showed nimesulide to

be a more potent analgesic than aspirin (data on file, Helsinn).

In the phenyl-p-benzoquinone writhing model in mice, Böttcher et al. (1987) found that the activity of nimesulide was less pronounced than that of indomethacin, piroxicam and diclofenac sodium. However, in the acetic acid writhing model in rats, indomethacin, piroxicam, diclofenac sodium and nimesulide were shown to have similar activity.

In another study, nimesulide (5 mg/kg orally) produced 50% inhibition of the writhing response to intraperitoneal injection of phenylquinone in mice, and was about 5 times more potent than aspirin (Swingle & Moore 1984).

2.2 Activity in Other Analgesia Models

In the Randall-Selitto assay, as modified by Swingle et al. (1971), the oral ED₅₀ of nimesulide was 5.2 (4.8 to 5.8) mg/kg. This was about 25 times the potency of aspirin and 5 times that of dextro-propoxyphene (Swingle & Moore 1984).

In the yeast-induced hyperaesthesia assay in rats, orally administered nimesulide produced an increase in the reaction threshold to pressure of the inflamed rat paw. The ED₅₀ (95% confidence limits) was 5.2 (4.8 to 5.6) mg/kg. In comparison, the ED₅₀ (95% confidence limits) for aspirin, determined by Riker Laboratories, was 76 (37 to 154) mg/kg. In this assay, nimesulide did not affect the reaction threshold to pressure of the noninflamed paw (data on file, Helsinn).

2.3 Reduction of Yeast-Induced Hyperthermia

Nimesulide produced a statistically significant reduction in the yeast-induced hyperthermia in rats when compared with controls (data on file, Helsinn). In a similar model, Böttcher et al. (1987) showed that the antipyretic activity of nimesulide was similar to that of indomethacin, diclofenac sodium and piroxicam.

Swingle and Moore (1984) found that oral doses of nimesulide 1.0 to 30 mg/kg significantly reduced the hyperthermia induced in rats by subcutaneous

aspirin (data on
writhing model
and that the ac-
counted than that
diclofenac sod-
writhing model
diclofenac sod-
to have similar

5 mg/kg orally)
writhing response
phenylquinone in
more potent than

Models

as modified by
of nimesulide
about 25 times
that of dextro-
(1984).
assay in rats,
produced an in-
pressure of the
confidence lim-
comparison, the
aspirin, deter-
76 (37 to 154)
did not affect the
the noninflamed

Hyperthermia

cally significant
hyperthermia in rats
ata on file, Hel-
er et al. (1987)
y of nimesulide
acin, diclofenac

d that oral doses
ificantly reduced
by subcutaneous

injection of yeast and that nimesulide was more
potent than phenylbutazone in this assay.

References

Bottcher I, Schweizer A, Glatt M, Werner H. A sulphonamido-
indanone derivative CGP 28237 (ZK 34228), a novel non-ster-
oidal anti-inflammatory agent without gastro-intestinal ulcero-
genicity in rats. *Drugs Under Experimental and Clinical Re-
search* 13: 237-245, 1987

Swingle KF, Grant TJ, Kvam DC. Quantal responses in the Ran-
dall-Selitto assay. *Proceedings of the Society for Experimental
Biology and Medicine* 137: 536, 1971

Swingle KF, Moore GGL. Preclinical pharmacological studies with
nimesulide. *Drugs Under Experimental and Clinical Research*
10: 587-597, 1984

Correspondence and reprints: Professor *G.P. Velo*, Istituto di Far-
macologia, Universita' di Verona, 37143 Verona, Italy.