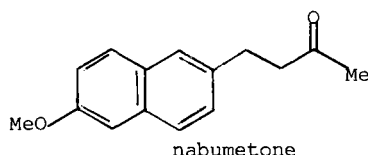


NABUMETONE - A NEW ANTI-INFLAMMATORY AGENT

E.A. Boyle, A.C. Goudie, F.R. Mangan, K. Randall, M.J. Thomson & A.P. Green, Beecham Pharmaceuticals, Research Division, Medicinal Research Centre, Harlow.

Nabumetone is a novel anti-inflammatory drug which in the laboratory displays anti-inflammatory, analgesic and anti-pyretic activity coupled with a freedom from gastric irritancy.



The structure/activity relationships of nabumetone and its analogues have shown that compounds possessing a small lipophilic group such as methoxyl, chloro or methyl in the 6 position in conjunction with a butan-2-one chain in the 2 position of the naphthalene ring were most active. Alkyl branching or extension of the side chain were deleterious whereas good activity was generally retained by forming esters of a butan-2-ol side chain.

A major feature of nabumetone is that it is non-acidic as presented to the stomach. This property, coupled with its poor ability as a prostaglandin synthetase inhibitor probably accounts for it being well tolerated by the gut. Table 1 shows results obtained for nabumetone and several comparative drugs in the carrageenin induced oedema model (Winter et al 1962) and a model of gastric irritancy in fasted rats (Hitchens et al 1967). A ratio of the dose which produces gastric damage in half of the dosed rats (GTD50) divided by the dose calculated to have reduced the oedema value by 25% also in half the animals (ED50) is included. In both tests a minimum of 8 rats per dose level and 3 levels of each drug were used. It can be seen that this ratio is much greater for nabumetone than for any of the other drugs.

Table 1 - Anti-inflammatory and gastric irritancy data for nabumetone and several comparative drugs

| Compound | Anti-inflammatory activity ED50 in mg/kg + 5% fiducial limits | | Gastric irritancy GTD50 in mg/kg + 5% fiducial limits | | Ratio of GTD50/ED50 |
|--------------|---|---------------|---|-----------------|------------------------|
| Nabumetone | 12.0 | (6.8 - 21.0) | 255 | (113.3 - 573.8) | 21.25 |
| Zomepirac | 2.1 | (0.5 - 8.4) | 16.5 | (7.2 - 38.0) | 7.86 |
| Fenbufen | 17.5 | (7.29 - 42.0) | 69.0 | (36.3 - 131.1) | 3.94 |
| Tolmetin | 10.0 | (4.4 - 23.0) | 30.0 | (14.3 - 63.0) | 3.00 |
| Naproxen | 2.5 | (1.1 - 5.5) | 7.0 | (4.5 - 10.9) | 2.80 |
| Piroxicam | 1.6 | (0.53 - 4.8) | 4.0 | (2.3 - 7.0) | 2.50 |
| Diclofenac | 6.8 | (1.94 - 23.8) | 4.9 | (2.0 - 12.0) | 0.72 |
| Indomethacin | 4.9 | (3.0 - 7.9) | 2.7 | (1.5 - 4.9) | 0.55 |
| Aspirin | 167 | (98 - 284) | 68.8 | (50.8 - 92.6) | 0.41 |

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