

General pharmacology, pharmacokinetics, and toxicology of nedocromil sodium

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The pharmacokinetic properties of nedocromil sodium give this agent a high safety margin in the treatment of asthma. Only 5% to 10% of an inhaled dose is absorbed, primarily from the respiratory tract, but also from the secondary oral route. Nedocromil sodium has very rapid plasma clearance and is confined to the extravascular space. The drug is not metabolized in either humans or animals, which renders animal testing relevant to the safety of this compound in humans. Tests conducted in several models did not uncover any adverse effects, even at high infused or inhaled doses. Also, nedocromil did not appear to interact with a variety of other drugs that are likely to be used concomitantly. These data support the long-term use of nedocromil sodium at doses required for therapeutic efficacy. (J ALLERGY CLIN IMMUNOL 1993;92:200-2.)

Nedocromil sodium is a salt of a water-soluble hydrophilic organic acid ionized at pH values of the human body. These properties, together with this drug's lack of reactive chemical groups, dictate its disposition and toxicology.

DISPOSITION

Nedocromil is not metabolized in animal species or in humans.¹⁻³ Although the drug is readily absorbed from the respiratory tract, only 5% to 10% of an inhaled dose is absorbed through the gastrointestinal tract. That percentage is usual for this route of administration. Total absorption of an inhaled dose in animals and in humans is typically the sum of entry to the respiratory tract (the primary route for nedocromil) and the oral route (the secondary route).

Absorption of nedocromil sodium is not slow, but it is not so rapid as clearance from the body. This property results in "flip flop" pharmacokinetics. In other words, the terminal plasma half-life is a measure of the rate of absorption, primarily from the lung, and not the elimination rate. Plasma clearance of the compound is very rapid and ranges from more than 300 ml/min/kg in the mouse to 10 ml/min/kg in humans. This variation is related to body weight and is consistent with the properties of other compounds in this class. Because it is an organic acid, nedocromil sodium is

modestly but reversibly bound to plasma proteins. However, it does not appear to have an affinity for any tissues other than those in the excretory organs—the liver and kidneys. Biliary and renal clearance occurs in different proportions, depending on the species. Enterohepatic recirculation is not a feature of this drug.

Nedocromil sodium appears to be largely confined to the extravascular space and poorly penetrates the CNS, the placental barrier, and milk. No metabolism has been detected in any animal species, including humans. From these considerations, it appears that tests in animal species are relevant to the assessment of the compound's safety in humans. Furthermore, other routes of administration (e.g., subcutaneous) are relevant in the assessment of the compound's parenteral toxicology. In fact, the subcutaneous route was used in all of the reproductive studies to ensure a high level of systemic exposure to the compound.

PHARMACOLOGY

Nedocromil sodium is active in several in vivo and in vitro models believed to be relevant to its therapeutic use.⁴ Of these models, the inhibition of response to specific antigen challenge in ascaris-sensitized monkeys in vivo and the inhibition of mediator release in antigen-challenged bronchoalveolar lavage cells from monkeys and humans are believed to be the most relevant. Nevertheless, the compound is also active in several other models, such as the rat, where effects include passive cutaneous anaphylaxis, passive lung anaphylaxis, mast cell degranulation, and mediator release from peritoneal mast cells.

From Fisons plc, Pharmaceutical Division.

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TABLE I. Main preclinical animal studies

Species	Duration	Route of administration	Type of study	Top dose mg/kg/day	Multiple of maximum human daily dose*
Rat	Single dose	Oral/intravenous	Acute toxicity	4000	14300
	1 mo	Intravenous	Toxicity	120	430
	1 mo	Subcutaneous	Toxicity	180	640
	3 mo	Inhalation†	Toxicity	30	110
	6 mo	Inhalation	Toxicity	36	130
	24 mo	Inhalation	Oncogenicity/toxicity	25	90
	Segment 1	Subcutaneous	Reproduction/multi-generation	100	360
	Segment 2	Subcutaneous	Reproduction/teratology	100	360
	Segment 3	Subcutaneous	Reproduction/perinatal	100	360
	Postweaning	Subcutaneous	Sexual development	100	360
Mouse	21 mo	Oral (diet)	Oncogenicity	180	640
Rabbit	Segment 2	Subcutaneous	Reproduction/teratology	100	360
Dog	14 days	Intravenous	Toxicity	80	290
	3 mo	Inhalation	Toxicity	6	20
	6 mo	Inhalation	Toxicity	20	70
	6 mo	Subcutaneous	Toxicity	40	140
	12 mo	Inhalation	Toxicity	10	35
	12 mo	Subcutaneous	Toxicity	20	70

*Multiple based on milligrams per kilogram of body weight. Maximum human maintenance dose = 2 inhalations (1.75 mg per actuation), four times daily, in a 50 kg person = 0.28 mg/kg.

†Rat inhalation studies used a nose-only technique.

Nedocromil sodium was also tested in a wide range of pharmacologic studies that were designed to reveal potential adverse effects of the compound. Various body systems were monitored, including the CNS, gastrointestinal, respiratory, and cardiovascular systems. In summary, nedocromil sodium appears to have few effects, even at high infused or inhaled doses. There were some short-lived but potent effects on the cardiovascular systems of certain animal species: transient hypotension in the dog (the Bezold-Zarish reflex) and transient hypertension in rabbits and guinea pigs. These effects, especially the Bezold-Zarish reflex in the dogs, are believed to be species specific and have not been observed in humans. The compound did not appear to interact to any significant degree with a variety of other drugs that are likely to be used concomitantly.

TOXICOLOGY

Nedocromil sodium has a very low order of toxicity.⁵ Doses far larger than those that would be used in humans are required to elicit any short-term toxic effects. The administration of the

compound has been tested by a variety of routes (primarily inhalation) in rodent and other species for up to 2 years. The repeated-dose toxicity studies included single-dose applications in several species and the following tests in rats: 1-month intravenous administration, 1-month subcutaneous administration, 3 months' inhalation, 6 months' inhalation, and 24 months' inhalation. The 24-month study assessed both toxicity and carcinogenicity and used dosages up to approximately 25 mg/kg/day. The following tests were performed on dogs: 14 days' intravenous administration, 3 months' inhalation, 6 months' combined inhalation and subcutaneous administration, and 12 months' inhalation and subcutaneous administration (with dosages up to 20 mg/kg/day). A second carcinogenicity study in mice involved oral administration of dosages up to 180 mg/kg/day. In addition to these trials, a full range of reproductive studies (including teratology in rat and rabbit) was carried out with a top dosage of 100 mg/kg/day by subcutaneous administration. A battery of mutagenicity tests was performed, together with other special tests that were designed to elicit any adverse effects on a

variety of systems, including host defense. None of these studies revealed adverse effects of nedocromil sodium at any of the dose levels used. Some short-term effects were noted in single-dose studies in which doses of 2 gm/kg or more were given intravenously (Table I).

On the basis of evidence gathered in animal studies, nedocromil sodium appears to be extremely well tolerated. No potential has been identified for long-term toxic effects on any organ or body system, nor does there appear to be any potential for genotoxic or carcinogenic activity. Moreover, this compound has not demonstrated any adverse effects on the reproductive system or on the normal development of growing animals (from weaning to maturity).

CONCLUSION

In conclusion, nedocromil sodium has a high safety margin. The animal safety data are believed to be relevant to assess safety in humans and support the long-term use of the compound at doses required for therapeutic efficacy. Nedocromil sodium does not appear to have the potential

for causing significant adverse effects by means of exaggerated (or high-dose) pharmacology. The compound has several beneficial effects on a variety of cells and in other test systems relevant to the pathogenesis of asthma.

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An overview of human safety data with nedocromil sodium

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The pharmacokinetic characteristics of nedocromil sodium suggest that this new antiinflammatory agent will be a very safe treatment for asthma. Nedocromil sodium is absorbed from the lung; very little is absorbed from the gastrointestinal tract. It is not metabolized and thus will not compete for metabolic pathways. Nedocromil sodium is not protein bound at a level at which it will displace other compounds. Rapidly cleared from plasma, nedocromil sodium has a very nar-

row range of general pharmacologic effects. Moreover, it has an extremely low level of toxicity in animal models. As described by Dr. Clark at this workshop, the lack of toxicity in animals at doses many magnitudes of the human dose demonstrates a large margin of safety for this drug.

Clearly, what happens in humans is most important, and our means of determining a clinical profile for any drug come from the results of clinical studies. Nedocromil sodium is generally well tolerated. More than 8400 patients have participated in both double-blind controlled and open-label clinical trials of the drug ranging from 2 to 52 weeks. Of these, 5352 patients received nedocromil sodium, 3538 on a four times daily schedule and 1814 on either a twice-daily schedule or some other dose regimen. Approximately 73% of the patients used the study treatment for at least 8 weeks. Adverse events occurring in

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